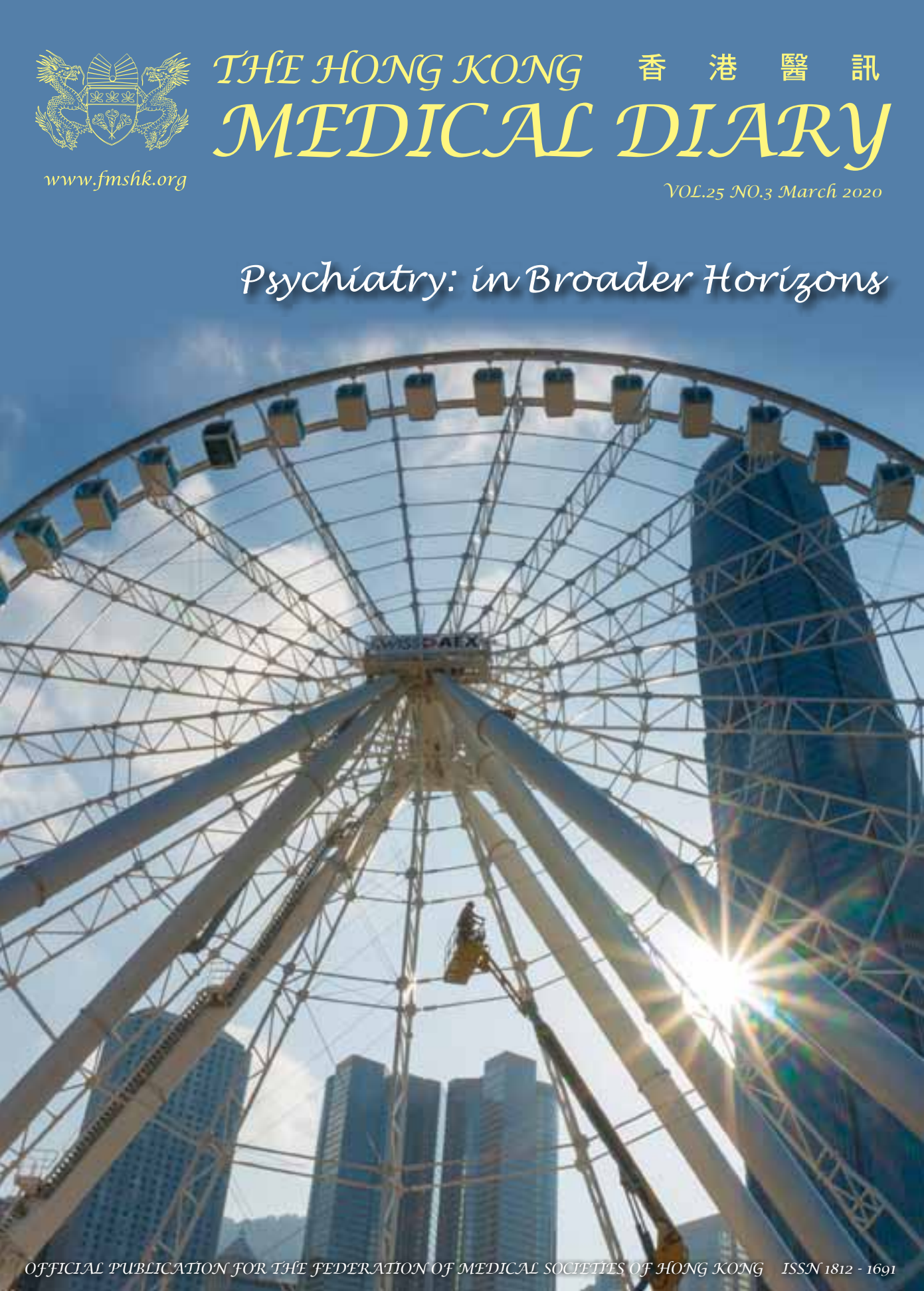
www.fmshk.org

THE HONG KONG MEDICAL DIARY

香 港 醫 訊

VOL.25 NO.3 March 2020

Psychiatry: in Broader Horizons



OFFICIAL PUBLICATION FOR THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG ISSN 1812 - 1691

Make Way for Possibilities in Schizophrenia

REXULTI® delivered short- and long-term efficacy across the spectrum of schizophrenia[1,2]

- REXULTI® demonstrated significant improvement in PANSS score in patients with acute schizophrenia[1]
- 86.5% of patients remained relapse-free in a 52-week study[2]
- REXULTI® maintained improvements in general functioning as measured by GAF[2]

REXULTI® is an atypical antipsychotic indicated for the treatment of schizophrenia.

PANSS = Positive and Negative Syndrome Scale GAF = Global Assessment of Functioning

Abbreviated Prescribing Information

REXULTI (Brexpiprazole) 0.5mg/1mg/2mg/3mg tablets. **INDICATION:** Schizophrenia in adults. **DOSAGE:** Starting dose for brexpiprazole is 1 mg once daily on days 1 to 4. Target dose range 2 mg to 4 mg once daily. Based on the patient's clinical response and tolerability, dose can be titrated to 2 mg once daily on day 5 through day 7 and then to 4 mg on day 8. Maximum daily dose 4 mg. Refer to Package Insert for switching from and to brexpiprazole. For moderate to severe renal and hepatic impairment, maximum daily dose reduced to 3 mg. Reduce dose in patients who are CYP2D6 poor metabolizers and for concomitant use with CYP2D6/CYP3A4 inhibitors. Adjust dose for concomitant use with CYP3A4 inducers. **CONTRAINDICATION:** Hypersensitivity to the drug and its excipients. **WARNINGS AND PRECAUTIONS:** Close supervision of high-risk patients for occurrence of suicidal behavior. Use with caution in patients with cardiovascular disorders. QT prolongation. Venous thromboembolism. Orthostatic hypotension and syncope. Cease treatment upon signs and symptoms indicative of neuroleptic malignant syndrome or unexplained high fever. Use with caution in patients with history of extrapyramidal symptoms. Dose reduction or cease treatment at signs and symptoms of tardive dyskinesia. Higher incidence of cerebrovascular adverse reactions in elderly patients with dementia and treatment not recommended for these patients. Monitor hyperglycaemia, weight gain and dyslipidaemia. Seizures. Disruption of the body's ability to reduce core body temperature. Dysphagia. Higher risk of impulse control disorders in patients with prior history. Leukopenia, neutropenia and agranulocytosis. Elevated prolactin levels. Not to be used in patients with hereditary galactose intolerance, total lactase deficiency or glucose galactose malabsorption due to lactose contained. Pregnancy: not recommended. **ADVERSE REACTIONS:** Rash, weight increase, akathisia, dizziness, tremor, sedation, diarrhea, nausea, abdominal pain upper, back pain, pain in extremity, increased blood prolactin and creatine phosphokinase. **DRUG INTERACTIONS:** Predominantly metabolized by CYP3A4 and CYP2D6. Refer to Package Insert for dose adjustment for concomitant use with CYP inhibitors and inducers. Please see full Prescribing information for details. (HKOP_REXULTI API_HK Revised Jan 2019)

HKOP-REX-2019-004

References: 1. Kane JM, Skuban A, Ouyang J et al. *Schizophr Res.* 2015 May;164(1-3):127-35.
2. Fleischhacker WW., Hobart M., Ouyang J. et al. *Int J Neuropsychopharmacol.* 2017 Jan 1; 20(1): 11–21.

For the product's safety, contraindications and side effects and toxic hazards, please refer to the package insert. Further information is available upon request.

REXULTI® brexpiprazole tablets

Otsuka Otsuka Pharmaceutical (H.K.) Ltd.
21/F, East Exchange Tower, 38 Leighton Road, Causeway Bay, Hong Kong. Tel: 2881 6299 Fax: 2577 5206

Contents

Scan the QR-code

To read more about The Federation of Medical Societies of Hong Kong

Disclaimer

The Cover Shot

The happiness of the Ferris wheel 幸福摩天輪

Ferris wheel is Hong Kong's iconic tourist attraction. Each cabinet of this Ferris wheel may hold an individual, a family, or a group of friends. As a whole, the Ferris wheel represents the Hong Kong community.

Nowadays, being a mental health worker is akin to being a maintenance worker of a Ferris wheel. We need to broaden our horizons. Not only do we need to take care of the mental wellbeing of individuals, we should also pay attention to the mental health of the entire Hong Kong society. Mental health workers are not just limited to psychiatrists, who count on collaborative support of other medical professionals as well as allied health professionals. May we join hands to promote the mental health of Hong Kong and may our Ferris wheel keeps wheeling bringing to us hope and happiness!

Dr Ivan WC MAK

MBChB (HK), MRCPsych (UK), FHKCPsych, FHKAM (Psychiatry), DCPsyc RCP&S (Irel), MSc (Epidemiology and Biostatistics; CUHK), GradDipFamMed (Monash)

Specialist in Psychiatry

Published by
The Federation of Medical Societies of Hong Kong

Design and Production
A-PRO MULTIMEDIA LTD www.apro.com.hk

Editorial

Dr Chi-wing LAW

MBBS (HK), MRCPsych (UK), FHKCPsych, FHKAM (Psychiatry)

Specialist in Psychiatry
Associate Consultant, Department of Psychiatry, Queen Mary Hospital

Editor

Dr Chi-wing LAW

In 2017, the World Psychiatric Association (WPA) and the Lancet Psychiatry have commissioned a team of medical professionals, researchers, and service users around the globe to draft a new commission on the future of psychiatry. It is believed that in the first quarter of this century, psychiatry is at the cusp of major changes. In this commission, several priority areas in the 21st century in the field of psychiatry have been identified and addressed. Among them, the importance of knowledge on the anatomy and physiology of the brain as it relates to complex behaviours, thoughts and emotions and more importantly, the effect of social factors on these processes, have been identified as being essential in understanding the pathophysiology of psychiatric disorders. Further advances in neuroscience would likely transform the way psychiatric disorders are being diagnosed and treated.

In this commission, the role of psychiatrists in society has also been stressed, particularly in the way of working with the communities. These could involve general mental health promotion and prevention activities, or focus on particular groups at risk. Digital psychiatry is another priority area that has been addressed in the commission. Given the exponential pace of technological advances, the commission would offer immense potential for radical changes in terms of service delivery as well as the development of new alternatives for psychiatric treatment.

In the light of these streams of ideas, I treasure this opportunity being offered as the issue editor in making this issue of Medical Diary a platform to explore the potentials of the psychiatric specialty in various horizons including medical science, treatment and societal aspects. I have the honour to invite a few researchers and clinicians to contribute their expert and invaluable knowledge and experiences over these areas.

I have invited Professor Michael Wong, who has been running a territory-wide specialised clinic on neuropsychiatric disorders, to give us an overview in the concepts, history and development, as well as a few illuminating case examples in this area. His article is followed by my attempt to give a review of a patient with autoimmune encephalitis, which I have encountered in my work as a consultation-liaison psychiatrist, as another illustration of a neuropsychiatric disorder. The potential in the development of innovative novel treatment options, apart from current pharmacological and psychological interventions, for psychiatric disorders have been described by Dr PW Cheng with his reaearch experience in this field.

In exploring the horizon of the role of psychiatrists in societal perspective, I have invited Dr KT Chan, who has expertise in studying the relationship between culture and psychiatry, to give us another thought-provoking overview on the topic of digitalisation, which is an inevitable trend in the coming generation, and its impact on the specialty of psychiatry. I hope this article could serve as a starter in stimulating our thoughts over this important area in the coming decades, with an impact not only restricted to the psychiatric specialty but indeed extended to the medical profession as a whole. Dr Sherry Chan, who is an expert clinician and researcher in the field of early

psychosis, has kindly shared her precious experience in utilising the platform of informative technology in her iPEP internet-based psychoeducation programme to exemplify the possibility of telepsychiatry in the future. While we have exploration in the field of digitalisation and telepsychiatry in the modern era, Dr WC Yan has given a review on a film on shamanism in the lifestyle section, to let us visualise resemblance of psychiatric practice at the other end of spectrum in the more ancient and traditional aspect of our culture.

After witnessing what has been going through in our society in the past few months, which I had never imagined while drafting the initial contents of this theme issue in mid-2019, I have also invited Dr Ivan Mak, Chairman of the Public Awareness Committee of the Hong Kong College of Psychiatrists, to give a comprehensive review and update on the topic of post-traumatic stress disorder. The review has been written as an additional token of the contribution of the psychiatric specialty to the medical profession and to the society of Hong Kong as a whole.

References

Bhugra D., Tasman A., Pathare S., et al. The WPA-Lancet Psychiatry Commission on the Future of Psychiatry. Lancet Psychiatry 2017; 4: 775-818

Neuropsychiatry in the 21st Century

Prof Michael TH WONG

MBBS MD (HK), MA MDiv (MST), PhD (Monash), FRCPsych, FRANZCP, FHKAM (Psychiatry), AFRACMA, FISCAST

Specialist in Psychiatry
Clinical Professor, Department of Psychiatry, LKS Faculty of Medicine, The University of Hong Kong

Prof Michael TH WONG

INTRODUCTION

For decades if not centuries, neurological disorders have been regarded as disorders of the brain and psychiatric disorders those of the mind. Nowadays they are increasingly viewed as being on the same neuropsychiatric spectrum. Common neuropsychiatric disorders include those with prominent emotional, cognitive, perceptual and behavioural symptoms such as neurodegenerative disease, epilepsy, cerebrovascular disease, traumatic brain injury, movement disorders and autoimmune disorders such as anti-NMDAR encephalitis.

At one end of the spectrum are those with predominantly motor disturbance such as Parkinson's Disease (PD) while those at the other end exhibit predominantly mental disturbance such as schizophrenia, bipolar disorder, depression and anxiety. Between them are those with various combinations of motor and mental disturbance such as multiple sclerosis, epilepsy and stroke with different degrees of gross neuropathology and/or pathophysiology. Overlaps of motor and mental symptoms are indeed common along the entire spectrum. Up to 36% of patients with PD show some evidence of cognitive impairment at disease onset, and another 40% of these patients developed depression over time.[1,2] Four types of overlap have been observed – neurological disorder presenting with psychiatric symptoms, psychiatric disorder presenting with neurological symptoms, a neurological disorder causing a psychiatric reaction and psychiatric disorder causing a neurological reaction.[3]

Neuropsychiatrists focus on disorders of the brain and mind which are associated with gross brain pathologies and/or dysfunctions in neural circuits and neurotransmitters. These disorders manifest not only as a disturbance in psychomotor, cognitive, emotional and volitional processing but also as the impairment of a person's interaction with other persons and the world. Unlike people with healthy brains and minds who display flexible thought and behaviour in meeting the demands of daily life, patients with these disorders struggle to adapt to various challenges in their physical and social environment.[4]

Neuropsychiatry is therefore not Consultation Liaison (CL) Psychiatry which deals with the psychiatric aspects of various medical and surgical conditions and is, therefore, broader in her concern and more eclectic in her approach. Neuropsychiatry is also not Behavioral Neurology which limits her concern to abnormal behaviour or experience with demonstrable brain pathology and is hence not inclusive of all psychiatric disorders. Those who are involved in Biological Psychiatry are not neuropsychiatrists but are essentially neuroscientists specialised in various biological aspects of psychiatric disorders such as genomics, neurochemistry, histology, electrophysiology, endocrinology, immunology, pharmacology and brain imaging. Many neuropsychiatrists, however, are also clinical neuroscientists with active research involvement in one or more areas of biological psychiatry.

Neuropsychiatry is not a new discipline. Trimble dated the origin of neuropsychiatry to the Renaissance and the Enlightenment when exploration of brain anatomy noted that brain lesions and pathology had something to do with conditions such as epilepsy, syphilis, movement disorders and hysteria.[5] Neuropsychiatry was very active in the 19th century. Alois Alzheimer who identified pre-senile dementia was a psychiatrist and neuropathologist. This interest in and the work on the study of the brain in the practice of psychiatry was however eclipsed around the same time by the psychodynamic theory of Sigmund Freud on unconsciousness and dreams which led to psychiatry that split the mind from the brain. It was not until around the 1980s when the interaction between mind and brain in the expression of psychiatric symptoms was given the attention that she deserves again.[6] Neuropsychiatry in her present form is, therefore, a modern endeavour, dealing with clinical presentations at the interface between psychiatry, neurology and general medicine. In this narrow sense, it represents the clinical discipline which manages patients with the psychiatric manifestation of neurological and general medical and surgical disorders. In the broader sense, it represents the practice of psychiatry informed by various advances in clinical neuroscience.

LATEST DEVELOPMENTS IN NEUROPSYCHIATRY

Research in clinical neuroscience over the past two decades have provided support to the notion of the neuropsychiatric spectrum. Postmortem pathological changes have been identified in the hippocampus in schizophrenia[7] and the anterior cingulate cortex in major depressive disorder.[8] Decreased amygdala-hippocampal reactivity follows administration of selective serotonin reuptake inhibitor (SSRI) and increased dorsolateral prefrontal cortex, and cingulate gyrus activation follows that of norepinephrine

reuptake inhibitors.[9] Deep brain stimulation (DBS) of the subgenual anterior cingulate cortex (Brodmann area 25), ventral striatum, and nucleus accumbens has shown potential efficacy in alleviating treatment-resistant depression.[10]

Neuropsychiatry, however, sees psychiatric disorders are better framed as disorders of distributed interconnected brain networks involving the pre-frontal-subcortical brain circuits rather than as disorders of discrete localised pathology as commonly found in neurological disorders.[11] Prefrontal regions include the dorsolateral prefrontal cortex, anterior cingulate cortex and orbitofrontal cortex each with discrete basal ganglia and thalamic connections and primarily involved in higher-order cognitive and or affective functions.[12] Impairments of anterior cingulate cortex-subcortical circuit cause the motivational deficit, orbitofrontal cortex-subcortical circuit disinhibited behaviour, and dorsolateral cortex-subcortical circuit dysexecutive symptoms.[13]

It is therefore very important to distinguish clinical discrete lesion-based psychopathology such as post-stroke depression from those limited circuit based pathologies such as frontal network syndromes as seen in patients with dementia and traumatic brain injuries as well as those widely distributed network-based dysfunctions such as default mode, salience, attention, emotional processing, cognitive control, social cognitive, memory and visceral-somatic processing[14] which can be potentially targeted by emerging treatment modalities such as Transcranial magnetic stimulation (TMS) and DBS.[15]

A recurrent theme among neuropsychiatrists and clinical neuroscientists is that we have to move beyond simplistic localisation toward a model of distributed modular functions integrated through structural and functional connectivity, adding neural circuitry to the classic biopsychosocial formulation and integrating research findings in neural plasticity and epigenetics to provide mechanisms that mediate organism-environment interactions in the context of neurodevelopment, including the notion of risk and resilience and intervention that may alter illness trajectory.[16]

The National Neuroscience Curriculum Initiative[17] has been set up to develop this culture of embracing cognitive-affective neuroscience and neuropsychiatry to expedite the "bench-to-bedside" translation of brain-symptom relationship to help guide clinical thinking and future innovative therapeutic interventions through more precise brain-behaviour correlate and informed prediction, prevention, rehabilitation and recovery of psychiatric disorders. To achieve this aim, the ability to synthesise and translate research findings and put them into a patient's individual context is required, without making the error of reductionism (that is to depict a person as nothing but just the brain) and oversimplification (that is localising specific mental function to a single brain structure or specific region rather than to a neural network). Clinical judgment is needed to decide when a worry has become anxiety, unhappiness depression, enthusiasm mania and memory dysfunction dementia and when to formulate a personalised narrative that is more therapeutic than medications like in a grief reaction and when to carefully document cognitive and functional impairment in order to organise a psychosocially appropriate care as in Alzheimer's Disease.

NEUROPSYCHIATRIC SPECTRUM – A TALE OF THREE LADIES

Here are three case vignettes to illustrate what the neuropsychiatric spectrum is like in real life. They all have been de-identified to ensure confidentiality.

A is an 18 year-old waitress who presented with mixed depressive and anxiety symptoms. She has been well all along until four years ago when she became increasingly distractible and forgetful. She started to have episodes of staring look for up to 10 minutes. Her personality changed from being outgoing to socially withdrawn. Two years later she started to throw things around unprovoked. Her father described her as if she was "in another world". These temper tantrums occurred nearly weekly, and all were quite similar and without warning. She would turn quiet and sometimes walked away and 10 minutes later she would become fearful and tremulous, saying "don't go away … I'm scared…". Her parents usually have to hug her to calm her down. She cried every time and took up to 30 minutes to calm down. She had to lie down to rest afterwards and only had a vague recollection of what had happened. During and after these episodes she heard voices which were numerous, male and female, talking to her directly, asking her to kill herself. She was initially diagnosed as having depression before her psychotic symptoms became apparent; she was put on an antidepressant but she became manic. Her mania was controlled with antipsychotic medications, but she started to hear voices all the time and even between episodes – multiple, male and female, third person, doing a running commentary on her thoughts and actions. Six months later she tried to jump from a height but was stopped in time. She developed the unshakable beliefs that people were following her and trying to kill her. She required multiple hospital admissions. Examination showed no localising neurological signs but there were persistent auditory hallucinations and delusions of reference and persecution. Her executive functions were reduced in speed but her cognition was otherwise normal. EEG on two occasions showed generalised slow waves and multifocal spikes. MRI brain scan was normal. She was diagnosed as having complex partial epilepsy. Her psychosis was initially ictal and postictal and later inter-ictal. She was put on the anticonvulsant Sodium Valproate and the antipsychotic Amisulpride. She showed noticeable but only partial improvement.

B is a 55 year-old single unemployed woman who presented with her first episode of psychosis. She had a stroke (dominant lobe) when she was 40 complicated by epilepsy, which responded to the anticonvulsant Sodium Valproate. She underwent renal transplant when she was 42 but had to start peritoneal dialysis two years later and switched to haemodialysis seven years after that. On one occasion, when her urea and potassium levels worsened, she developed delusion of reference that people everywhere were talking about her

for no good reasons. She had no perceptual disturbance and was in clear sensorium. She became clinically anxious and depressed. She did not have any localising neurological signs. She had nominal dysphasia, impaired 3-minute recall and reduced speed in executive function. Her cognitive function was otherwise normal. She was diagnosed to have delusional disorder. EEG showed non-specific slow waves but no spikes. Her symptoms partially remitted with the improvement of her electrolytes and commencement of the antipsychotic Risperidone. She declined antidepressant. Her mental state worsened later when she stopped her antipsychotic but improved again when she agreed to go back on it.

C is a 25 year-old cleaner who started to hear voices and see visions a year ago. She was a victim of sexual assault by a stranger and of physical and emotional abuse by her mother when young. She was a frequent target of bullying at school. She had a problem paying attention in class, especially when she was picked on by other students or confronted by her teachers. Her mind just "went numb" although she "could still hear and see but could not feel a thing".

Sometimes the passage of time seemed to slow down. She had to pinch or scratch herself to get out of that unpleasant state. More recently, she started to see and hear at times characters from movies or comic books and at other times her abusive mother and bullies back in her school days; such experiences made her very angry and wanted to cut herself. She felt that these characters were there to harm her. She could not be sure if these voices and visions were in her head or not, but they were very vivid and real to her. She could no longer cope with work. She became depressed and anxious, losing interest, motivation and energy and having a problem with her sleep. She felt suicidal but did not have any plan. Neurological and cognitive assessment were both normal. EEG and brain scan were normal. She was diagnosed to have major depressive disorder. Her perceptual disturbance and her mind going numb are actually the consequence of her previous traumas which have sensitised her to stress and that in turn makes her go into a dissociative state. She has responded to antidepressant and has found praying with her friends at church very comforting, but her dissociation requires further post-traumatic counselling.

These three patients experience anxiety and depression with disturbance of their perception and with ideas or beliefs that people are talking about them and/or planning to harm them. From the brain-symptoms correlate perspective, their depressive symptoms can be partially localised to the anterior cingulate cortex and related striatal-thalamic subcortical components. Their negative cognition is suggestive of impaired modulation of negative mood states and is compatible with changes at the subgenual cingulate cortex and the amygdala. Their anhedonia can also be localised to the anterior cingulate cortex-subcortical circuit, particularly the ventral striatum/nucleus accumbens. Their cognitive slowing suggests a mild dysexecutive syndrome of lateral prefrontal dysfunction localisable to the dorsolateral prefrontal cortex. Their mixed anxiety and depressed presentation are compatible with the fact that these two symptoms share the fronto-limbic substrate.[18] Their individual clinical histories, however, have their own particular biopsychosocial features and require more than brain-mind correlate to make full sense. The epilepsy in A is the precipitating and now the perpetuating factor for her psychosis. The previously well-controlled epilepsy and the brain compromised by an old infarct in B have likely been destabilised by her electrolyte imbalance precipitating a psychotic episode which improves with treatment but deteriorates when antipsychotic was stopped. The childhood traumatic experience of C has predisposed her to cortical hyperexcitability which could have been misinterpreted as epilepsy and psychosis without a careful neuropsychiatric assessment and meticulous clarification and detailed documentation of psychopathology which uncovers very different pathophysiology that benefits from spiritual support and requires psychotherapy in addition to pharmacotherapy.

THE FUTURE OF NEUROPSYCHIATRY

Despite the advocacy of Engel[19] for a biopsychosocial approach to psychiatry in general and that of Lishman a balanced and comprehensive perspective for neuropsychiatry in particular, psychiatry continues to tend to go from one extreme to the other, what Eisenberg[20] calls the unfortunate swing from "brainlessness" (neglecting neurobiology) to "mindlessness" (over-focusing on neuroscience) and on top, her ongoing ambivalence to and negligence of culture, religion and spirituality.[21]

As long as we are mindful of these potential pitfalls in the practice of neuropsychiatry and clinical neuroscience as discussed above, we should be able to go from strength to strength. In the area of nosology, we should be able to stay clear from either reductionism (nothing but the brain) or dualism (brain and mind are separate and different) and have an integrative approach to the disorders of the brain and mind. The never-ending advances in neurobiology and cognitive science will continue to refine our explanation of psychopathology. Seeing psychiatric disorders as not only just brain disorders but also disorders of social relationship and environmental/ecological adaptation will open up opportunities for us to develop a concept of illness that upholds a sophisticated understanding of the complex interplay between symptoms, behaviour and function in the experience and expression of mental illness and health and wellbeing. The fact that we have evidence for neuroplasticity and that mental forces can transform brain matter, such as cognitive-behavioural therapy (CBT) can change brain patterns to the benefit of patients with obsessive-compulsive disorder (OCD) and depressive disorders[22] or childhood abuse and bullying and acute and chronic stress may have a permanent impact upon brain organisation and behavior[23], there is a good chance for new therapeutics that goes beyond medications and surgery to non-invasive psychosocial interventions which can fine-tune our brain and mind. Last but not least any further and ongoing dialogues between neuropsychiatry, clinical neuroscience and philosophy of science and psychiatry will facilitate the formulation of psychiatric ethics that is informed by neuroscience of ethics which not only explain our brain more but also help us understand our mind better.

References

1. Foltynie T, Brayne C, Robbins T et al: The cognitive ability of an incident cohort of Parkinson's patients in the UK: The CamPaiGN Study. Brain 2004; 127: 550-560.
2. Mollenhauer B, Weintraub D. The depressed brain in Parkinson's Disease: implications for am inflammatory biomarkers. Proceedings of the National Academy of Sciences 2017; 14:3004-3005.
3. Zeman A. Neurology is psychiatry – and vice versa. Practical Neurology 2014; 14:136-144.
4. Glannon W. Psychiatric neuroethics – studies in research and practice. Oxford: Oxford University Press, 2019.
5. Trimble MR. The intentional brain: motion, emotion and the development of modern neuropsychiatry. Baltimore, MD: Johns Hopkins University Press, 2016.
6. Lishman A. What is neuropsychiatry? Journal of Neurology Neurosurgery & Psychiatry 1992; 55(11): 983–985.
7. Harrison PJ. The hippocampus in schizophrenia: a review of the neuropathological evidence and its pathophysiological implications. Psychopharmacology 2004; 174:151-162.
8. Cotter D, Mackay D, Landau S et al. Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. Archives of General Psychiatry 2001; 58:543-553.
9. Outhred T, Hawkshead BE, Wager TD et al. Acute neural effects of selective serotonin reuptake inhibitors versus noradrenaline reuptake inhibitors on emotion processing: implications for differential treatment efficacy. Neuroscience and Biobehavioral Review 2013; 37: 1786-1800.
10. Holtzheimer PE, Kelley ME, Gross RE et al. Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. Archives of General Psychiatry 2012; 69:150-158.
11. Ressler KJ, Mayberg HS. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. National Neuroscience 2007; 10(9): 1116-1124.
12. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annual Review of Neuroscience 1986; 9:357-381.
13. Bonelli RM, Cummings JL. Frontal-subcortical circuitry and behavior. Dialogues in Clinical Neuroscience 2007; 9:141-151.
14. Shao J, Meng C, Tahmasian M et al. Common and distinct changes of default mode and salience network in schizophrenia and major depression. Brain Imaging and Behavior 2018; 12(6): 170801719.
15. Uhlhass PJ. Neural dynamics in mental disorders, World Psychiatry 2015; 14:116-118.
16. Klengel T, Binder EB. Epigenetics of stress-related psychiatric disorders and gene x environment interactions. Neuron 2015; 86(6): 1343-1357.
17. National Neuroscience Curriculum Initiative– www.NNCIonline.org.
18. Torous J, Stern AP, Padmanabhan JL et al. A proposed solution to integrating cognitive-affective neuroscience and neuropsychiatry in psychiatry residency training: The time is now. Asian Journal of Psychiatry 2015; 17:116-121.
19. Engel GL. The need for a new medical model: a challenge for biomedical medicine. Science 1977; 196:129-136.
20. Eisenberg L. Mindlessness and brainlessness in psychiatry. The British Journal of Psychiatry 1986; 14:497-508.
21. Wong MTH. Ricoeur and the Third Discourse of the Person: From Philosophy and Neuroscience to Psychiatry and Theology. London: Lexington Books, 2019.
22. Yoshimura S, Okamoto Y, Onoda K et al. Cognitive behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self- referential processing. Social Cognitive and Affective Neuroscience 2014; 9:487-493.
23. Pitman RK, Rasmusson AM, Koenen KC et al. Biological studies of post-traumatic stress disorder. Nature Reviews Neuroscience 2012; 13:769-787.

Brain on Fire: A Patient with Autoimmune Encephalitis

Dr Chi-wing LAW

Dr Chi-wing LAW

MBBS (HK), MRCPsych (UK), FHKCPsych, FHKAM (Psychiatry)
Specialist in Psychiatry
Associate Consultant, Department of Psychiatry, Queen Mary Hospital

INTRODUCTION

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was first described in a case series of 12 women with ovarian teratomas by Dalmau and colleagues in 2007. In his group of patients reported, a wide range of symptoms, including prominent psychiatric symptoms, amnesia, dyskinesia, autonomic dysfunction, and decreased level of consciousness, were found.[1] This autoimmune condition was later found to be not exclusively paraneoplastic, and subsequent studies reported up to 70% of patients afflicted without any tumour involvement.[2]

In 2012, the book "Brain on Fire: My Month of Madness", an autobiography written by a young New York Post journalist suffering from this illness, was published.[3] The book was further adapted into a motion picture in 2016, which made this disorder known even to the general public subsequently.

Anti-NMDAR encephalitis was found to be the most common form of autoimmune encephalitis. It was also reported to have surpassed the frequency of any individual viral cause of encephalitis in young persons.[4] Since its discovery, the impact of this disorder in both specialties of neurology and psychiatry has been remarkable. People started pondering if there had been cases of such being misdiagnosed and thus mistreated as psychiatric conditions like psychosis or mood disorders in the past.

A CLINICAL SCENARIO

Miss X was a 20 year-old university student. She had complaint of abdominal pain and swelling for more than one month before the diagnosis of a right ovarian teratoma was subsequently ascertained. The operation was soon performed including right salpingo-oophorectomy (with the frozen section of right tube and ovary showing immature teratoma), followed by left ovarian cystectomy, as well as right pelvic and para-aortic lymphadenectomy. Subsequent sessions of chemotherapy were undertaken as well.

Since around the time of her operation, Miss X was aware of mild thought disturbance subjectively though the problem was not marked and did not cause any obvious disturbance in her normal life initially. More significant symptoms were, however, reported six weeks after the operation, with obvious abnormal mental state observed by her parents as well since then. After discussion of her problems with the gynaecologist, and subsequent assessment by a clinical psychologist, the care team decided to refer the patient to a consultation-liaison psychiatrist in the gynaecology ward for further assessment of possible psychiatric disorder.

During the psychiatric assessment, Miss X reported subjective difficulty in comprehension of others' speech. She often felt her thoughts being stuck. She found it hard to respond with appropriate answers during conversations. Her parents also noticed she was being inattentive and had a problem in carrying out a conversation. Her condition fluctuated from time to time. At one time when her mental state appeared to be most disturbed, she seemed to have difficulty in telling even the correct name of her mother.

Miss X also recalled experiences of hearing some vague voices coming from her mind on and off, though she could not describe their content clearly. She also experienced abnormal visual perceptions from time to time, like seeing changes in colours of objects around. She further reported difficulty in distinguishing events happening in reality versus in dreams at times.

Miss X described her mood being low at times after the operation but was not persistently depressed. She had worrying thoughts about her abnormal experiences and symptoms. She reported subjective difficulty in concentrating on mental activities such as reading, and she experienced decreased interest in her usual hobbies. She failed to continue with her study and worried that she would be unable to do so in the long run. Her quality of sleep had been suboptimal with easy awakening. Her appetite remained normal otherwise. She did not have any suicidal idea.

Miss X was noticed by her parents to have some facial twitching on and off. There was an episode of fainting which occurred at home days before the psychiatric consultation, and she was admitted to the medical ward. Investigations including blood tests and CT brain revealed no significant abnormality, and she was discharged after a brief stay.

During the interview by the psychiatrist, Miss X appeared calm, polite and cooperative. She had fair concentration and was able to give accurate yet brief general answers to questions on factual demographic and autobiographic information. When asked about more complex and abstract questions, she had more obvious difficulty to respond and tended to give more vague answers such as "I'm not sure". Her mood was

stable and described by herself to be mildly low. She otherwise did not have any negative thoughts or suicidal idea. She did not report any hallucination, abnormal perception, or any delusional belief at the time of assessment. She demonstrated satisfactory orientation. However, upon further screening for cognitive function using the Montreal Cognitive Assessment Hong Kong version (HK-MoCA), she scored 22/30 only (Normal cutoff 26/30).

After the psychiatric assessment, in view of her recent history of teratoma, fluctuating nature of cognitive function impairment and abnormal perceptions reported, and her fainting episode with seizure attack being a possibility, suspicion of a diagnosis of autoimmune encephalitis, particularly anti-NMDA receptor encephalitis, was raised. Other possible psychiatric differential diagnoses, including depressive disorder and at-risk mental state of psychosis, were also taken into consideration though.

A check of serum anti-NMDAR antibody was found to be negative. Other basic blood tests revealed no obvious abnormality. A brief generalised convulsion was however observed during her stay in the gynaecology ward. Miss X was then referred to the neurology team for further assessment and investigation. Electroencephalography (EEG) revealed slow activities over left temporal lobe, with no other abnormality. Lumbar puncture showed normal CSF glucose (3.9 mmol/L) and CSF protein (0.32 g/L). CSF anti-NMDAR antibody was however found to be positive. Cultures, MRI brain and PET-CT were all negative.

The neurology team prescribed a course of treatment of IVIG for the auto-immune condition and levetiracetam for seizure prophylaxis. No more seizure or twitching movement was noted. The patient reported gradual improvement in her cognitive function and resolution of her psychotic or mood symptoms. She was able to resume her study at the university after four months.

DISCUSSION

Anti-NMDAR encephalitis is a predominantly female condition (with a female to male ratio of around 8:2), with a median age of 27 years at presentation. The frequency of occurence is observed to be greatly reduced after 40 years of age. Psychiatric symptoms to a certain extent, are reported in up to 95% of patients. The psychopathology is found to be polymorphic in nature encompassing catatonia, mood, behaviour and psychosis domains.[2]

Clinical features of anti-NMDAR encephalitis are divided into three stages.[5] In 70% of patients, there could be a prodromal period, averaging five days but could be up to 2 weeks, of a viral-like illness with symptoms of headache, fever, malaise, myalgia, upper respiratory discomfort, nausea and diarrhoea.[6] Whether the prodromal symptoms are part of early immune activation or have resulted from a non-specific infection that facilitates the crossing of the blood-brain barrier by the immune response, is not clear.[7] In the second stage, early features are characterised by cognitive dysfunction, psychiatric features and seizures.[8] Seizure is a common presentation of anti-NMDAR encephalitis in children and young patients, in up to approximately 70% of patients.[9] The third stage is characterised by late features including reduced consciousness, involuntary movements, and autonomic dysfunction, which can occur as early as 10-20 days after the early features.[8] According to this scheme, our patient presented with mainly second stage early symptoms at the time of her psychiatric assessment.

In pathophysiological perspective, glutamate receptors (type NMDA) are located in the post-synaptic membrane and form heteromeric ligand-gated cation channels composed of NR1 and NR2 subunits.[10] Autoantibodies in the serum or CSF of patients with anti-NMDAR encephalitis were shown to bind specifically to an epitope located in the extracellular domain of the NR1 subunits.[7] There are striking similarities between anti-NMDAR encephalitis and other models of NMDAR-specific disruption, such as experimental and recreational use of phencyclidine and ketamine.[11] In other psychiatric conditions such as post-partum psychosis, there are also similarities in clinical presentations identified, thus shedding light into possible mechanism of reversible NMDAR-dominant receptor-mediated network disruption in these conditions secondary to alternative non-immune mechanisms.[2]

Diagnosis of anti-NMDAR encephalitis is based on the characteristic clinical symptoms, as well as supporting investigations including the brain MRI, EEG and CSF studies. Possible differential diagnoses include psychiatric conditions such as psychosis, affective disorder and substance-induced disorder. Other medical conditions such as infectious encephalitis (especially HSV) and other autoimmune etiologies (e.g. limbic encephalitis with autoantibodies against Hu, Ma2, CV2 and amphiphysin) should also be considered.[10]

In patients with anti-NMDAR encephalitis, CSF studies may review lymphocytic pleocytosis or oligoclonal bands. CSF protein can be elevated or normal, as in the case of our patient.[12] The diagnosis of anti-NMDAR encephalitis is confirmed by the detection of CSF antibodies against the GluN1 subunit of the NMDAR. Assays for serum anti-NMDAR antibodies are not as sensitive as CSF studies, with false-negative results in up to 14% of cases.[13] This was indeed the case found in our patient. Her serum anti-NMDAR was negative in the initial screening. Only in subsequent CSF studies performed was anti-NMDAR found to be positive.

EEG abnormalities may be identified in terms of focal or diffuse slow or disorganised activities. Epileptic activities may be revealed sometimes.[14] Extreme versions of the "delta brush pattern" in EEG, which are transient patterns characterised by a slow delta wave with superimposed fast activities, appeared to be unique to anti-NMDAR encephalitis and may suggest a more prolonged illness. It, however, was only seen in less than one-third of patients.[15] The EEG of our patient revealed only non-specific slow activities over left temporal lobe without other more specific abnormality. MRI is normal in 50% of the cases of anti-NMDAR encephalitis, as in our patient. Those with

abnormalities shown in MRI mostly involve non-specific T2 hyperintensity in the hippocampus, frontal and insular cortex.[16]

With regard to treatment, in those patients with teratoma being identified, tumour resection results in a noticeable neurological improvement in days or weeks in some of them. Immunotherapy is the treatment of choice with or without the presence of a tumour and involves trials of corticosteroids, intravenous immunoglobulins, or plasma exchange.[12]

Early identification and treatment of the condition are associated with better outcome.[9] Approximately 50% of patients are able to achieve full recovery. Yet more than 40% of patients continue to have mild to severe deficits. Up to 25% of patients may have severe deficits or even death.[7] Substantial, persistent cognitive impairments are found in some patients, particularly in the areas of executive function and memory. This observation is in line with the proposed pivotal role of NMDARs in the human brain. The good cognitive long-term outcome also depends on early and aggressive treatment, following which the patients are found to have less frequent hippocampal damage.[17]

A recent study has attempted to construct a grading score to predict neurologic function after diagnosis of anti-NMDAR encephalitis. Features including intensive care unit admission, treatment delay for more than 4 weeks of symptom onset, lack of clinical improvement within four weeks of starting treatment, abnormal brain MRI, as well as elevated CSF WBC count (> 20 cells/μL) are found to be independent predictors of poor functional status one year after symptom onset.[18]

As for our patient, the resection of her teratoma apparently failed to halt the progress of further development of the disorder. It is not clear if this early removal of the tumour led to relatively less severe symptoms observed in her case. To a certain extent, it was fortunate that her teratoma had been identified early due to relative prominent symptoms of abdominal pain and distension. This important piece of clinical information raised early suspicion of anti-NMDAR encephalitis as a possible diagnosis when only relatively non-specific psychiatric and cognitive symptoms were present at the early phase of her illness. The early confirmation of the diagnosis with appropriate investigations including CSF studies, and subsequent early initiation of appropriate intervention with immunoglobin therapy likely contributed to quicker remission of the disorder and satisfactory recovery of her cognitive function.

CONCLUSION

As discussed, anti-NMDAR encephalitis demonstrates a possible common mechanism of receptor-mediated network disruptions via different aetiology in neurological and psychiatric disorders. In the case of autoimmune encephalitis, "yellow flag" symptoms serving as warning signs of the condition have been suggested including decreased level of consciousness, abnormal postures or movements (orofacial, limb dyskinesia), autonomic instability, focal neurological deficits, aphasia or dysarthria, rapid progression of psychosis (despite therapy), catatonia, hyponatremia, headache, and presence of other autoimmune disease (e.g. thyroiditis).[19] As part of the assessment of patients with new-onset psychotic symptoms, vigilance is required to watch out for other medical conditions which may result in similar neurophysiological disruption disguising as a psychiatric condition. The emergence of atypical symptoms are alarming features in particular.

References

1. Dalmau J., Tüzün E., Wu HY., et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007; 61(1): 25-36
2. Al-Diwani A., Handel A., Townsend L., et al. The psychopathology of NMDAR-antibody encephalitis in adults: a systematic review and phenotypic analysis of individual patient data; Lancet Psychiatry. 2019; 6: 235-246
3. Susannah Cahalan. Brain on Fire: My Month of Madness. Simon & Schuster Paperbacks
4. Dalmau J. & Graus F., Antibody-mediated encephalitis. N Engl J Med 2018; 378: 840-851
5. Sharma B., Handa R., Prakash S., et al. Anti-NMDA receptor encephalitis: A neurological disease in psychiatric disguise; Asian J Psychiatry. 2014; 7: 92-94
6. Kayser MS. & Dalmau J., Anti-NMDA receptor encephalitis in psychiatry; Curr Psychiatry Rev. 2011; 7(3): 189-193
7. Dalmau J., Gleichman AJ., Hughes EG., et al. Anti-NMDA receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurology. 2008; 7(12): 1091-1098
8. Irani SR., Bera K., Waters P., et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain. 2010; 133(6): 1655-1667
9. Titulaer MJ., McCraken L., Gabilondo I., et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013; 12(2): 157-165
10. Wandinger K-P., Saschenbrecker S., Stoecker W., et al. Anti-NMDA-receptor encephalitis: A severe, multistage, treatable disorder presenting with psychosis. J Neuroimmunol. 2011; 231: 86-91
11. Vinckier F et al., Gaillard R., Palminteri S., Confidence & psychosis: a neuro-computational account of contingency learning disruption by NMDA blockade. Mol Psychiatry. 2016; 21(7): 946-955
12. Ford B., McDonald A., Srinivasan S., et al., Anti-NMDA receptor encephalitis: a case study and illness overview. Drug in Context. 2019; 8: 212589
13. Gresa-Arribas N., Titulaer MJ., Torrents A., et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. Lancet Neurol. 2014; 13(2): 167-177
14. Dalmau J., Armangué T., Planagumà J., et al. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms & models; Lancet Neurol. 2019; 18(11): 1045-1057
15. Schmitt SE., Pargeon K., Frechette ES., et al. Extreme delta brush: A unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology. 2012; 79 (11): 1094-1100
16. Dalmau J., Lancaster E., Martinez-Hernandez E., et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurology. 2011; 10(1): 63-74
17. Finke C., Kopp UA., Prüss H., et al. Cognitive deficits following anti-NMDA receptor encephalitis. J Neurol Neurosurg Psychiatry. 2012; 83(2): 195-198
18. Balu R., McCracken L., Lancaster E., et al. A score that predicts 1-year functional status in patients with anti-NMDA receptor encephalitis. Neurology. 2019; 92(3): e244-e252
19. Herken J & Prüss H. Red flags: clinical signs of identifying autoimmune encephalitis in psychiatric patients. Front Psychiatry. 2017; 8: 25

Wellbutrin XL™ 24 HOUR
bupropion hydrochloride

gsk

Patients with MDD* often lose pleasure in those everyday activities they used to love

Which of the following concern do you commonly see in MDD* patients?

Fatigue

Loss of interest

Weight gain

Sexual dysfunction

Help patients rediscover their love for life

Consider Bupropion in MDD* patients because,

- The only dual acting antidepressant to target noradrenaline and dopamine[1]
- Greater improvement in sleepiness and fatigue scores compared to SSPI[2]
- No association with weight gain compared to placebo[3]
- Lower incidence of sexual side-effect compared to SSRIs[4]

Recommended by guidelines† as **1st line drug** *for patients with MDD**

Bupropion is associated with a dose-related risk of seizures. Wellbutrin XL should be discontinued and not restarted in patients who experience a seizure while on treatment.

Remarks: * MDD = Major Depressive Disorder † Guidelines are including WFSBP (World Federation of Societies of Biological Psychiatry) for biological treatment of unipolar depressive disorder 2013, Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines for mood disorders 2015, and CANMAT (Canadian Network for Mood and Anxiety Treatments) 2016 Clinical Guidelines for the management of adults with Major Depressive Disorder.

REFERENCES: 1. Fava M et al, 15 Years of Clinical Experience With Bupropion HCl:From Bupropion to Bupropion SR to Bupropion XL. Prim Care Companion J Clin Psychiatry 2005;7(3):106-13. **2.** Cooper JA et al Resolution of sleepiness and fatigue: A comparison of bupropion and selective serotonin reuptake inhibitors in subjects with major depressive disorder achieving remission at doses approved in the European Union J Clin Psychopharmacol 2014;28(2):118-124. **3.** Croft H et al . Effect on Body Weight of Bupropion Sustained-Release in Patients with Major Depression Treated for 52 Weeks. Clin Ther 2002;24(4):662-72. **4.** Thase ME et al. Remission Rates Following Antidepressant Therapy With Bupropion or Selective Serotonin Reuptake Inhibitors: A Meta-Analysis of Original Data From 7 Randomized Controlled Trials. J Clin Psychiatry 2005; 66(8):974-981

WELLBUTRIN XL™ Abbreviated Prescribing Information

INDICATIONS AND USAGE Treatment of major depressive disorder and prevention of seasonal major depressive episodes in patients with a diagnosis of seasonal affective disorder. **DOSAGE AND ADMINISTRATION** General Dosing Considerations: Insomnia may also be minimized by avoiding bedtime doses. WELLBUTRIN XL Tablets should be swallowed whole and not crushed, divided, or chewed. **Major Depressive Disorder:** The usual adult target is 300 mg/day, given once daily in the morning. Dosing should begin at 150 mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately tolerated, an increase to the 300-mg/day target dose, given as once daily, may be made as early as day 4 of dosing. There should be an interval of at least 24 hours between successive doses. As with other antidepressants, full antidepressant effect of WELLBUTRIN XL may not be evident until 4 weeks of treatment or longer. An increase in dosage to the maximum of 450 mg/day, given as a single dose, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. **Seasonal Affective Disorder:** Dosing should begin at 150 mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately tolerated, the dose of WELLBUTRIN XL should be increased to the 300-mg/day dose after 1 week. If the 300-mg dose is not adequately tolerated, the dose can be reduced to 150 mg/day. The usual adult target dose for WELLBUTRIN XL Tablets is 300 mg/day, given once daily in the morning. For patients taking 300 mg/day during the autumn-winter season, the dose should be tapered to 150 mg/day for 2 weeks prior to discontinuation. **CONTRAINDICATIONS** Patients with hypersensitivity to bupropion or any of the other components of the preparation; patients with a seizure disorder; patients undergoing abrupt discontinuation of alcohol or sedatives; patients currently being treated with any other preparation containing bupropion as the incidence of seizure is dose dependent; patients with a current or previous diagnosis of bulimia or anorexia nervosa. Concomitant use of WELLBUTRIN XL and monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse between discontinuation of MAOIs and initiation of treatment with WELLBUTRIN XL tablets. **WARNINGS AND PRECAUTIONS** Clinical Worsening and Suicide Risk with Psychiatric Disorders: Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Screening Patients for Bipolar Disorder:** Serious neuropsychiatric symptoms have been reported. A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. **Seizures:** Bupropion is associated with a dose-related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection. Should be discontinued and not restarted in patients who experience a seizure while on treatment. Patient factors: Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, central nervous system (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications (e.g., antipsychotics, antidepressants, theophylline, systemic steroids) that lower seizure threshold. Clinical situations: Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin. Retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized if the total daily dose of WELLBUTRIN XL does not exceed 450 mg and the rate of incrementation of dose is gradual. **Impaired hepatic function:** WELLBUTRIN XL should be used with extreme caution in patients with severe hepatic cirrhosis. WELLBUTRIN XL should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis. All patients with hepatic impairment should be closely monitored for possible adverse effects that could indicate high drug and metabolite levels. Impaired renal function: Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. WELLBUTRIN XL should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered as bupropion and the metabolites of bupropion may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible adverse effects that could indicate high drug or metabolite levels. **Paediatric Use:** Safety and effectiveness in the pediatric population have not been established. Anyone considering the use of WELLBUTRIN XL in a child or adolescent must balance the potential risks with the clinical need. **Geriatric use:** Reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **Cardiovascular Effects:** In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These events have been observed in both patients with and without evidence of preexisting hypertension. There is no clinical experience establishing the safety of WELLBUTRIN XL Tablets in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. **Pregnancy:** WELLBUTRIN XL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** Bupropion and its metabolites are secreted in human milk. Decision should be made whether to discontinue nursing or to discontinue the drug. **INTERACTIONS** The potential exists for a drug interaction between WELLBUTRIN XL and drugs that are substrates of or inhibitors/inducers of the CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, cyclophosphamide, ticlopidine, and clopidogrel). Coadministration of bupropion with drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (SSRIs and many tricyclics, e.g., nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index. Drugs which require metabolic activation by CYP2D6 in order to be effective (e.g. tamoxifen) theoretically could have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion. Although citalopram is not primarily metabolized by CYP2D6, in one study bupropion increased the Cmax and AUC of citalopram by 30% and 40%, respectively. In a series of studies in healthy volunteers, ritonavir (100 mg twice daily or 600 mg twice daily) or ritonavir 100 mg plus lopinavir 400 mg (Kaletra®) twice daily reduced the exposure of bupropion and its major metabolites in a dose dependent manner by approximately 20 to 80%. Similarly, efavirenz 600 mg once daily for two weeks reduced the exposure of bupropion by approximately 55%. This effect of ritonavir/Kaletra® and efavirenz is thought to be due to the induction of bupropion metabolism. Patients receiving any of these drugs with bupropion may need increased doses of bupropion but the maximum recommended dose of bupropion should not be exceeded. Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine in 12 healthy volunteers. Administration of WELLBUTRIN XL to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, There have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with bupropion. The consumption of alcohol during treatment with WELLBUTRIN XL should be minimized or avoided. False-positive urine immunoassay screening tests for amphetamines have been reported in patients taking bupropion. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish bupropion from amphetamines. Serotonergic psychiatric drugs should not be started in a patient receiving linezolid. Wait until 24 hours after the last dose of linezolid before starting the serotonergic psychiatric drugs. **EFFECTS ON ABILITY TO DRIVE AND USE MACHINE** Until they are reasonably certain that WELLBUTRIN XL do not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery. **ADVERSE REACTIONS** WELLBUTRIN XL has been demonstrated to have similar bioavailability both to the immediate-release formulation of bupropion and to the sustained-release formulation of bupropion. The information included under this subsection is based primarily on data from controlled clinical trials with WELLBUTRIN SR Tablets, the sustained-release formulation of bupropion. The following adverse events have been reported with a frequency of ≥1/100 to 1/10 (common) and ≥1/10 (very common). Immune system disorders Hypersensitivity reactions such as urticaria. Metabolic and Nutrition disorders anorexia. Psychiatric disorders Insomnia, agitation and anxiety. Nervous System disorder Headache, tremor, dizziness and taste disorders. Eye and labyrinth disorders Tinnitus. Ear and labyrinth disorders Tinnitus. Vascular disorders increased blood pressure (sometimes severe), flushing. Gastrointestinal disorders dry mouth, gastrointestinal disturbance including nausea and vomiting, abdominal pain, constipation. Skin and subcutaneous tissue disorders rash, pruritus, sweating. General disorders and administration site conditions: fever, chest pain, asthenia. **OVERDOSE** Seizures, hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses. Deaths associated with overdoses of bupropion alone have been reported in patients ingesting large doses of the drug. **Treatment:** Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Activated charcoal should be administered. No specific antidotes for bupropion are known. Abbreviated Prescribing information based on version GDS22. Please read the full prescribing information prior to administration. Full prescribing information is available on request from GlaxoSmithKline Ltd, 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong

GlaxoSmithKline Limited
Hong Kong Branch 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong. Tel: (852) 3189 8989 Fax: (852) 3189 8931
Macau Branch Avenida Infante D. Henrique, No.43-53A, Edf. Macau Square 21 andar C, Macau. Tel: (853) 2871 5569 Fax: (853) 2871 5987
hk.gsk.com

HKRX/BHC/0001/18 (06/2020)
Date of preparation: 11/07/2018

New 21st Century Intervention in Psychiatry - Non-Invasive Brain Stimulation (NIBS): Potential and Future Development

Dr Pak-wing CHENG

MBBS (HK), FHKCPsych, FHKAM (Psychiatry)

Specialist in Psychiatry

Clinical Assistant Professor, Department of Psychiatry, LKS Faculty of Medicine, The University of Hong Kong

Dr Pak-wing CHENG

INTRODUCTION

Pharmacological treatment and psychotherapy are the two main streams of treatment modalities in modern psychiatry. However, there are limitations to each kind of treatment modality, including the side effects of the medications, the labour intensity and cost-ineffectiveness of psychotherapy, and the non-responsiveness or inadequate response to both modalities. Therefore, new options for treatment modality has become a pressing issue in the field of psychiatry.

Looking back at psychiatric history, invasive psychosurgery where a specific brain area is targeted was once viewed as a cure for mental illness in the mid-20th century. However, inadequate understanding of neuroscience and the invasive nature of psychosurgery resulted in poor treatment outcomes, and thus this treatment modality gradually faded out. Only electroconvulsive therapy (ECT), which requires general anaesthesia, remains commonly used in the clinical setting for treatment-resistant depression and psychotic disorders. In contrast, deep brain stimulation (DBS) for refractory depression and obsessive-compulsive disorder (OCD) is rarely used in the clinical setting.

In recent decades, non-invasive brain stimulation (NIBS) has been under the spotlight in mental health research. The most common forms of NIBS are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). With the advancement of neuroscience, mental illness nowadays is viewed as a kind of brain disorder. Specific brain areas or networks are believed to contribute to the pathophysiology of those disorders. Therefore, if we could target specific brain abnormalities, it would be possible to cure or alleviate the symptoms without causing generalised side effects from non-specific approaches. The recent development of neurostimulation and neuro-navigation techniques has allowed us to target specific brain areas or networks with direct electric current, induced electric current or ultrasound shock wave, to modulate activities at the cellular level and change the neuroplasticity. Another advantage of this treatment modality is that it is usually well-tolerated without the need for general anaesthesia. Some patients might experience mild and transient physical discomfort such as headache, itchiness and redness, but only a few people have experienced a seizure in TMS.

TMS AND ITS APPLICATION

TMS uses an electromagnetic field to induce an electric current within the brain.[1] Repetitive TMS (rTMS) delivers a train of pulses at the same intensity over time at a particular region of the brain. It either stimulates or suppresses neuronal activity, depending on the frequency and the inter-train interval between pulses. The effect of rTMS is mediated by modulating the neuronal activities of the targeted dysfunctional area. Distributed modulation of brain activities via a specific brain network may also be achieved.[2] The clinical effects of rTMS may be affected by many factors, including the number of sessions, the intensity level of pulses, the interval between sessions, and the position and shape of the coil.

TMS has been most studied in the treatment of depression. For adults with depression and on whom antidepressants have failed, application of high-frequency rTMS over the dorsolateral prefrontal cortex (DLPFC) for 4-6 weeks daily, usually five times per week, is a standard treatment protocol approved by the U.S. Food and Drug Administration (FDA) in 2008. In recent years, the FDA has approved a newer treatment parameter of TMS using theta-burst stimulation, which has the advantage of shorter treatment time.

Apart from depression, the FDA also approved deep TMS as a treatment of OCD in 2018, based on a randomised, multi-centre study of 100 patients. In the study, 38% of OCD patients had more than 30% reduction in symptoms, according to the Yale-Brown Obsessive-Compulsive Scale (YBOCS).[3] The specific TMS coil was used to achieve deep penetration in the brain. High-frequency deep TMS was applied to the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC) region to target the dysfunction of the cortico-striato-thalamo-cortical (CSTC) circuit, which is the underlying pathophysiology of OCD.[4]

TMS has also been applied to patients with cognitive impairment,[5] anxiety disorder and post-traumatic stress disorder (PTSD)[6] with promising results in some studies. However, conflicting evidence has been noted. Further larger-scale studies are needed to provide more evidence.

tDCS AND ITS APPLICATION

tDCS is a neurostimulation technique where a mild direct current (1-2 mA) is induced through the cerebral cortex via electrodes placed on the scalp, which in turn modifies cortical excitability, depending on the polarity

directions.[7] It is easier and cheaper to administer compared to TMS, and it can also be delivered at home. Its effects are possibly exerted through modulating cortical excitability.[8] Long-term plasticity is enhanced, with modulations in the rate of neurotransmitter release.[9]

The application of tDCS in clinical use is less supported by evidence. To date, there is not yet any FDA approval for tDCS for the treatment of any mental illness. tDCS studies are most commonly done on depression. In a recent meta-analysis of six randomised controlled trials (RCTs) with 289 adult patients, tDCS was shown to be significantly superior to sham-control treatment in response, remission and improvement in depression. In most studies, the left DLPFC was stimulated, and the effect size was comparable with those reported for antidepressant drug treatment and rTMS.[10] However, a recent large international RCT of adult patients with depression showed no difference in reducing depressive symptoms between active and sham stimulation in patients with unipolar or bipolar depression.[11] The conflicting results warrant further high-quality RCTs to determine the efficacy of tDCS.

Moreover, studies of tDCS on patients with schizophrenia, substances abuse disorders and OCD also showed promising initial results. Further larger-scale studies and meta-analysis, however, would be necessary to inform the effectiveness of tDCS in a clinical setting.[12]

EMERGING NIBS TECHNIQUE

Besides the aforementioned two most commonly investigated NIBS, there are new NIBS which use transcranial ultrasound to modulate brain activity. Compared with TMS and tDCS, this technique has a higher spatial resolution and can reach deeper structures.[13] Its safety profile is comparable to that of the other NIBS techniques. There are various modalities and names for this new technique, including transcranial focused ultrasound and transcranial pulse stimulation (TPS), also known as low-intensity extracorporeal shock wave therapy (Li-ESWT).

The underlying mechanism of this technique is mechanotransduction. It is a biological pathway through which the cells convert the mechanical TPS stimulus into biochemical responses.[14,15] It could affect neurons and induce neuroplastic effects through several pathways, including increasing cell permeability;[16] stimulation of mechanosensitive ion channels;[15] release of nitric oxide resulting in vasodilation; increased metabolic activity and angiogenesis;[17] stimulation of vascular growth factors (VEGF);[18] and stimulation of brain-derived neurotrophic factor (BDNF).[19]

Most of the existing studies have been done on healthy volunteers to test the neuromodulation effect in different parts of the brain, including the thalamus and basal ganglia. With the adjustment of stimulation parameters, it can cause the suppression or facilitation of neural activity.

Such a technique has also been applied to five patients with unresponsive wakefulness syndrome, resulting in significant improvement in their vigilance and oropharyngeal motor functions.[20] Another application is on Alzheimer's disease (AD). TPS was obtained with CE marking in 2018 for the treatment of the central nervous system (CNS) in patients with mild to moderate Alzheimer's disease (AD). In a recent study, TPS was applied to elderly patients with AD in three sessions (6000 pulses each) per week for 2-4 weeks, either over classical AD affected sites such as the dorsolateral prefrontal cortex, areas of the memory and language network, or overall accessible brain areas (global brain stimulation). Significant improvement in the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) score was demonstrated (immediately as well as 1 and 3 months after stimulation). fMRI also showed significantly increased connectivity within the memory network.[21]

Since this NIBS technique is still relatively new, further studies should be done with various disease groups before it can be applied in a clinical setting.

CONCLUSION

NIBS is a group of non-invasive neuromodulation techniques which are potentially useful to treat various mental illnesses such as depression, OCD, schizophrenia, substances abuse disorders and dementia. Their administration is easier, and their safety profile is better than traditional psychosurgery or deep brain stimulation. Their efficacy in some conditions such as depression and OCD has been proven to be comparable to pharmacological treatment. NIBS has great potential to be a new treatment option for the 21st century, as monotherapy or adjuvant therapy to existing treatment. Further effort in researching this area will provide more evidence of the effect of these NIBS techniques in clinical use.

References

1. Wassermann, E. M., & Lisanby, S. H. (2001). Therapeutic application of repetitive transcranial magnetic stimulation: a review. Clinical Neurophysiology, 112(8), 1367-1377.
2. Rotenberg, A., Horvath, J. C., & Pascual-Leone, A. (Eds.). (2014). Transcranial magnetic stimulation. New York: Springer.
3. https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-transcranial-magnetic-stimulation-treatment-obsessive-compulsive-disorder
4. Carmi, L., Alyagon, U., Barnea-Ygael, N.,et al. (2018). Clinical and electrophysiological outcomes of deep TMS over the medial prefrontal and anterior cingulate cortices in OCD patients. Brain stimulation, 11(1), 158-165.
5. Cheng, C. P. W., Wong, C. S. M., Lee, K. K., Chan, et al. (2018). Effects of repetitive transcranial magnetic stimulation on improvement of cognition in elderly patients with cognitive impairment: a systematic review and meta-analysis. International journal of geriatric psychiatry, 33(1), e1-e13.
6. Gouveia, F. V., Gidyk, D. C., Giacobbe, P., et al. (2019). Neuromodulation strategies in post-traumatic stress disorder: From preclinical models to clinical applications. Brain sciences, 9(2), 45.
7. Nitsche, M. A., Boggio, P. S., Fregni, F.,et al. (2009). Treatment of depression with transcranial direct current stimulation (tDCS): a review. Experimental neurology, 219(1), 14-19.
8. Thorpe, S., Delorme, A., & Van Rullen, R. (2001). Spike-based strategies for rapid processing. Neural networks, 14(6-7), 715-725.
9. Das, S., Holland, P., Frens, M. A.,et al. (2016). Impact of transcranial direct current stimulation (tDCS) on neuronal functions. Frontiers in neuroscience, 10, 550.
10. Brunoni, A. R., Moffa, A. H., Fregni, F., et al. (2016). Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. The British Journal of Psychiatry, 208(6), 522-531.
11. Loo, C. K., Husain, M. M., McDonald, W. M.,et al. (2018). International randomized-controlled trial of transcranial Direct Current Stimulation in depression. Brain stimulation, 11(1), 125-133.

12. Kekic, M., Boysen, E., Campbell, I. C., et al. (2016). A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders. Journal of psychiatric research, 74, 70-86.
13. di Biase, L., Falato, E., & Di Lazzaro, V. (2019). Transcranial Focused Ultrasound (tFUS) and Transcranial Unfocused Ultrasound (tUS) Neuromodulation: From Theoretical Principles to Stimulation Practices. Frontiers in Neurology, 10.
14. Ingber, D. E. (2006). Cellular mechanotransduction: putting all the pieces together again. The FASEB journal, 20(7), 811-827.
15. d'Agostino, M. C., Craig, K., Tibalt, E., et al. (2015). Shock wave as biological therapeutic tool: from mechanical stimulation to recovery and healing, through mechanotransduction. International journal of surgery, 24, 147-153.
16. Zhang, J., Kang, N., Yu, X., et al. (2017). Radial Extracorporeal Shock Wave Therapy Enhances the Proliferation and Differentiation of Neural Stem Cells by Notch, PI3K/AKT, and Wnt/β-catenin Signaling. Scientific reports, 7(1), 15321.
17. Mariotto, S., Cavalieri, E., Amelio, E., et al. (2005). Extracorporeal shock waves: from lithotripsy to anti-inflammatory action by NO production. Nitric oxide, 12(2), 89-96.
18. Hatanaka, K., Ito, K., Shindo, T., et al. (2016). Molecular mechanisms of the angiogenic effects of low-energy shock wave therapy: roles of mechanotransduction. American Journal of Physiology-Cell Physiology, 311(3), C378-C385.
19. Wang, B., Ning, H., Reed-Maldonado, A., et al. (2017). Low-intensity extracorporeal shock wave therapy enhances brain-derived neurotrophic factor expression through PERK/ATF4 signaling pathway. International journal of molecular sciences, 18(2), 433.
20. Lohse-Busch, H., Reime, U., & Falland, R. (2014). Symptomatic treatment of unresponsive wakefulness syndrome with transcranially focused extracorporeal shock waves. NeuroRehabilitation, 35(2), 235-244.
21. Beisteiner, R., Matt, E., Fan, C., et al. (2019). Transcranial Pulse Stimulation with Ultrasound in Alzheimer's disease–A new navigated focal brain therapy. bioRxiv, 665471.

Dermatology Quiz

Dermatology Quiz

Dr Chi-keung KWAN

MBBS(HK), FRCP(Lond, Glasg), Dip Derm(Glasg), PDipID(HK), FHKCP, FHKAM(Med)

Specialist in Dermatology and Venereology

Dr Chi-keung KWAN

Fig. 1 Pigmented patch with satellite lesion on Lt forefoot

This 51 year-old Caucasian lady who was totally asymptomatic came to the clinic to have mole checking. Incidentally, a pigment patch was found on left sole. Further asking revealed the patch had been present for around three years. Since the patch was totally asymptomatic, the patient did not pay much attention to it. She just knew that the patch seemed increasing in size slowly. Physical examination revealed a 2.5 cm irregular pigmented patch on the left sole which was heterogeneous in colour and with suspected satellite lesions. The surface was smooth without any ulceration or erosion. (Fig. 1)

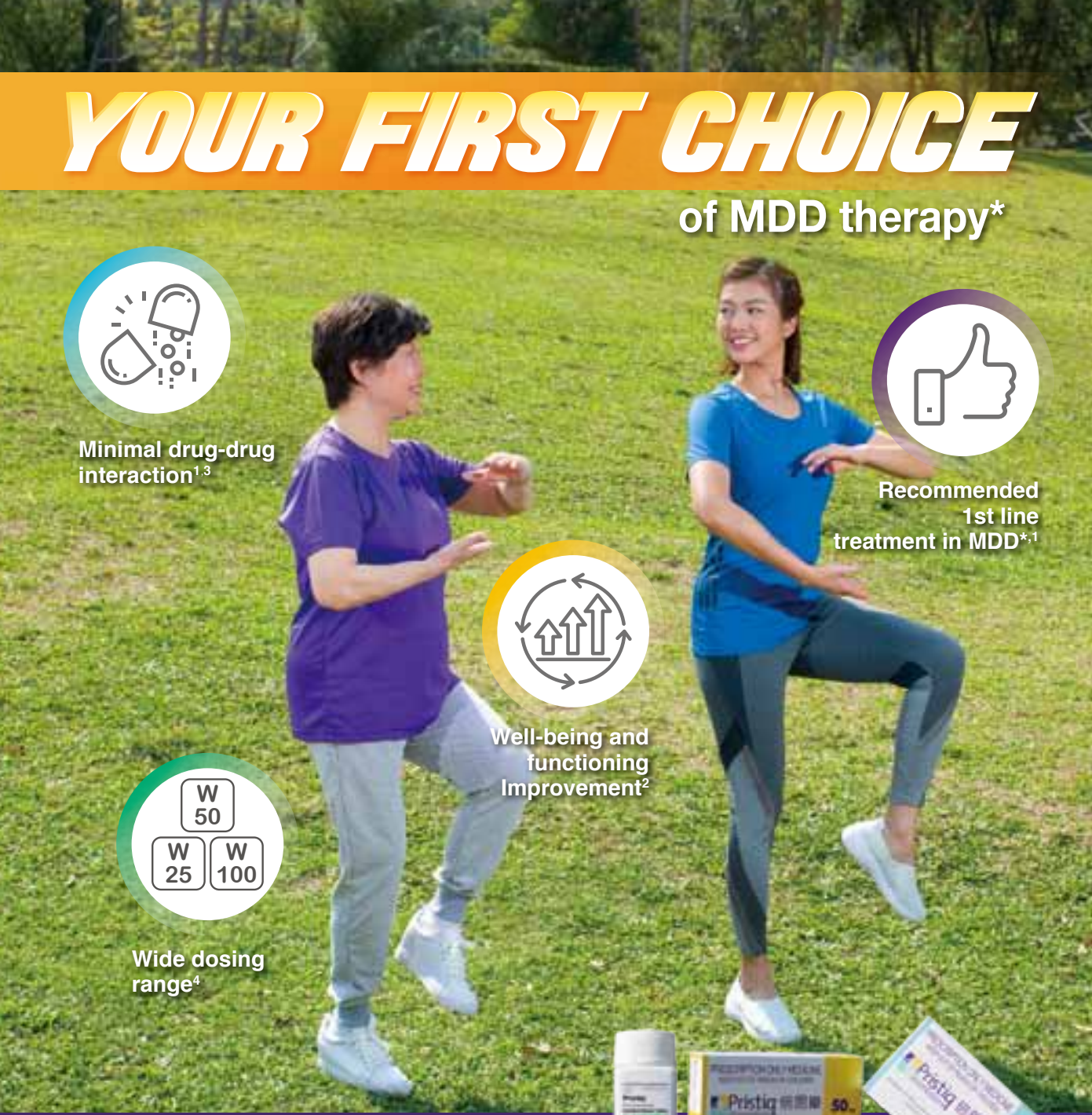
Questions

1. What are the differential diagnoses of his skin lesion?
2. What investigation are you going to order?
3. How do you treat this patient?

(See P.36 for answers)

YOUR FIRST CHOICE

of MDD therapy*



Minimal drug-drug interaction[1,3]

Recommended 1st line treatment in MDD*,[1]

Well-being and functioning Improvement[2]

Wide dosing range[4]

* SNRIs, the class of drugs to which Pristiq® belongs, is one of the first-line recommendations for pharmacotherapy for MDD[1].

MDD = major depressive disorder. SNRI = serotonin and noradrenaline reuptake inhibitor.

References

1. Kennedy SH, et al. Can J Psychiatry 2016;61:540-560. 2. Boyer P, et al. Int Clin Psychopharmacol 2008;23:243-253. 3. Low Y, et al. Neuropsychiatr Dis Treat 2018;14:567-580. 4. Pristiq® (desvenlafaxine) Prescribing Information. Pfizer Corporation Hong Kong Limited Version April 2018.

PRISTIQ® ABBREVIATED PACKAGE INSERT

1. TRADE NAME: PRISTIQ® **2.** PRESENTATION: 25mg, 50 mg and 100mg Extended-Release tablets **3.** INDICATIONS: Treatment of adults with major depressive disorder (MDD) **4.** DOSAGE & ADMINISTRATION: 50 mg once daily at approximately the same time, with or without food. The maximum recommended dose in patients with severe renal impairment or end-stage renal disease (ESRD) is 25mg every day or 50 mg every other day. Supplemental doses should not be given to patients after dialysis. The recommended dose in patients with moderate to severe hepatic impairment is 50 mg/day and dose escalation above 100 mg/day is not recommended. The 25mg per day dose is intended for a gradual reduction in dose when discontinuing treatment. **5.** CONTRAINDICATIONS: Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the Pristiq formulation. Use of MAOIs with Pristiq or within 7 days of stopping treatment of Pristiq. Use of Pristiq within 14 days of stopping a MAOI. Starting PRISTIQ in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome. **6.** WARNINGS & PRECAUTIONS: All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behaviour, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Not approved for use in treating bipolar depression. Cautions on Serotonin syndrome; activation of mania/hypomania; elevated blood pressure & increased risk of bleeding. Caution is advised to patients with pre-existing hypertension, cardiovascular, cerebrovascular conditions; angle-closure glaucoma; seizure; hyponatremia; interstitial lung disease & eosinophilic pneumonia; discontinuation syndrome. **7.** INTERACTIONS: MAOI; other serotonergic drugs; drugs that interfere with hemostasis; drugs that are primarily metabolized by CYP2D6; avoid alcohol consumption. False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking desvenlafaxine. **8.** PREGNANCY AND LACTATION: There are no published studies on Pristiq in pregnant women. There are risks associated with untreated depression in pregnancy and with exposure to SNRIs and SSRIs, including Pristiq, during pregnancy. Available limited data from published literature show low levels of desvenlafaxine in human milk, and have not shown adverse reactions in breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Pristiq and any potential adverse effects on the breastfed child from Pristiq or from the underlying maternal condition. **9.** SIDE EFFECTS: Most commonly observed adverse reactions in short-term fixed-dose studies were: nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders. **10.** DRUG ABUSE AND DEPENDENCE. Pristiq is not a controlled substance. Reference: HK PI (Version Date Apr 2018). Date of preparation: Apr 2019 Identifier number: PRIS0419. FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.

PP-PRO-HKG-0033 (06/2019) VB_DES_1841A

Pfizer Corporation Hong Kong Limited
18/F., Kerry Centre, 683 King's Road, Quarry Bay, Hong Kong.
Tel: (852) 2811 9711 Fax: (852) 2579 0599
Website: www.pfizer.com.hk

Pristiq® desvenlafaxine

Impact to Psychiatry in the Age of Digitalisation: Disease of the Mind from Understanding, Treatment to Transformation

Dr Kai-tai CHAN

MBChB (HK), MRCPsych (UK), FHKCPsych, FHKAM (Psychiatry)

Specialist in Psychiatry

Dr Kai-tai CHAN

INTRODUCTION

Since the coining of the term 'Psychiatry' by Johann Christian Reil in 1808[1], Psychiatry has been developing rapidly as a branch of modern medicine for the diagnosis, treatment and prevention of disease of the mind.

When we take some time to look back in the history of disease of the mind, as far back as the time of ancient Greece, around 400 BC, Hippocrates[2], the father of medicine, had revolutionalised medicine at that period, when his ideas and works were subsequently collected in the legendary Corpus Hippocraticum. By then, he and his followers had already been postulating about the brain as the organ of the mind as well as delineating diseases of the brain.

Two millenniums had passed.

With the dawn of the Scientific Revolution and the Age of Enlightenment, the discovery and understanding of the mind and the world embarked into a whole new world of evidence and rationality.

Among the many important theorisations, the conceptualisation of body-mind dichotomy by Descartes[3] had been well received in subsequent generations as the mainstream model in understanding the human body and mind.

At about the same time, as modern medicine and technology drastically advanced, doctors and scientists were able to have a more accurate and detailed delineation of the human brain.

Human civilisation continued to bloom.

About one century ago, in addition to the perspective of philosophy, the conceptualisation of the self and the mind was gradually drifting towards the areas of Psychiatry and psychoanalysis. On top of the Freudian structural and topographic models of the mind[4,5], Freud also postulated the possible role of intra-psychic conflicts in the formation of disease of the mind, with subsequent development of psychoanalysis as a form of therapeutic intervention.

Decades later in the twentieth century, the pioneering scientific understanding in the disease of the brain and mind, like the Dopamine Hypothesis of Schizophrenia in the causation of psychosis, and the progressive invention of evidence-based psychiatric treatment (including pharmacological treatment, Electro-convulsive Therapy (ECT) and psychotherapy), in combination with humanistic psychosocial interventions, has brought about promising improvement in treatment efficacy and quality of life of psychiatric patients.

In essence, such major and landmark leaps in Psychiatry have shifted the paradigm of Psychiatry from containing insanity to advocating hope and recovery, fundamentally converting the Age of Asylum to an Era of Treatment and Rehabilitation.

Concerning the birth and history of digitalisation, it was the ground-breaking ideas and works of Alan Turing around the time of World War II making him considered the father of theoretical computer science and artificial intelligence (AI)[6]. Subsequently, it only takes half a century for the world to realise the drastic impact of the Digital Revolution in the humankind.

When it comes to the first encounter of Psychiatry and digitalisation in human history, I think that it could have been the invention of MuCulloch-Pitts Unit[7], a basic subunit of the computer simulating the basic subunit of the brain, in the 1930s. It was actually the embodiment of the first tangible connection of AI and neuroscience, while neuroscience is the mainstay for us to explore our mind and the disease of the mind, for which Psychiatry is about.

MEDICINE AND PSYCHIATRY IN THE AGE OF DIGITALISATION

After the dawn of the Age of Digitalisation in the twentieth century, understandably but unexpectedly, digitalisation and AI have been transforming the delivery of healthcare unprecedentedly in the past few decades.

Together with other ground-breaking advances in biotechnologies, like gene therapy and nanotechnology, the inevitable and increasing perusal of digitalisation in Medicine and Psychiatry, currently mainly in the form of algorithms, big data and robotics, should be originally intended for improving our health and quality of life, relieving our suffering and prolonging our lives at a more efficient, sophisticated and extensive as well as less expensive way with this best tool in our history.

To the other extreme, in less developed countries where basic healthcare delivery is still compromised by limitation in resources and accessibility, digital clinical management and online consultations can be one of the readily available short-term solutions to such an imminent need of basic rights and humanity.

In fact, all these advances can be attributed to the evolution of Artificial Neural Network (ANN), as well as the invention of human-created algorithms and evidence-based programmes by researchers and clinicians.

Currently, the major forms of digitalisation in Medicine and Psychiatry would include processing of big data

in healthcare, telemedicine, telepsychiatry, as well as various digitalised tools in assessment, diagnosis, treatment and research.

TWO SIDES OF THE SWORD

Undoubtedly, the digitalisation of clinical care and healthcare delivery is bringing about many essential benefits to human beings, including the possibility of treating more patients as well as previously inaccessible patients, the delivery of personalised medical care with better efficacy and probably efficiency, the higher reliability in medical service delivery, the possibly better healthcare cost-effectiveness as well as the development of more quantified and co-ordinated healthcare systems.

These unprecedented advances in the history of modern medicine are due to the drastic improvement in terms of flexibility, speed, scale, decision-making and personalisation in the delivery of healthcare in the Age of Digitalisation.

On the other hand, the apparent disadvantage brought about by digitalisation that most people can readily think of would be the compromise of the human touch in the course of a therapeutic relationship, which is particularly indispensable in Psychiatry where empathy is therapeutic and essential.

At a deeper level, challenges to ethical issues could range from the handling of massive confidential healthcare data to the accountability for the clinical decisions made by AI.

There have already been even worries about the possibility of replacement of doctors by AI in future, which is essentially a perceived existential threat of our profession.

UNIQUE IMPACT OF DIGITALISATION IN PSYCHIATRY

Regarding the specific impact of digitalisation and AI to Psychiatry, due to various obvious reasons, it would be wider and deeper than other medical specialties, ranging from psychopathology, pathogenesis, presentation, diagnosis, nosology, treatment, clinical management and research, to ethics.

In Psychiatry, one of the major cornerstones in the understanding of the disease of the mind has been built on descriptive psychopathology, which involves phenomenology, observation and empathy with a process to achieve understanding and explanation[8]. However far our digitalisation can go in the end, in the first place, it would be fundamentally impossible for any standardised assessment tools (like checklists and questionnaires) nor any invented digital diagnostic tools to comprehend and understand psychiatric patients in the way a psychiatrist does.

In terms of presentation and diagnosis in Psychiatry, we can take schizophrenia as an example. The salient feature of schizophrenia is the disturbance in the boundary of self and differentiation of reality and non-reality. The increasing infiltration of digitalisation in our self might weaken our self-boundary in general, and the interpretation about specific schizophrenic symptoms in patients, like passivity experience and thought alienation, would need more detailed delineation in our clinical practice in due course. Moreover, we can imagine that the increasing dominance of virtual reality in our daily living would actually pose increasing difficulty for us in validating the psychotic symptoms reported by our patients, like referential ideation and paranoia. What is more, with our increasing sense of omnipotence in the virtual world, the possible altered sense of salience and personal significance might be difficult to be differentiated from the primary symptoms like delusional atmosphere in patients who have schizophrenia.

For the aspect of nosology, there have been on-going debates about the aetiology and classification of addiction disorder related to internet use. We are still not sure whether it is a condition related to impulsivity or compulsion, or both. It is recently put as the condition for further research in the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM V) as Internet Gaming Disorder. But the next question to ask would be, 'would internet addiction still be regarded as a disease if every one of us needs to survive in a 24/7 internet world?

For the pathogenesis of psychiatric disorders, psychosocial stressors have been identified as one of the major causes in the pathogenesis of different kinds of psychiatric disorders in a multi-factorial model. In such an increasing digitalised world as ours, it is also just natural that the stressors experienced in the virtual world can also cause mental problems in our 'real' or pre-existing world. Worse still, the influence of digitalisation would actually reach deep down to different levels of inner 'Self', which would be possibly causing profound adverse effects upon our mental health, heeding further timely research.

Recently, there have been even postulations of harm to our brain by the process of multi-tasking, a common daily practice in the Age of Digitalisation, through the possible excessive release of cortisol and adrenaline as well as disturbance of dopamine addiction loop[9]. Likewise, the possible resting function of the mind-wandering mode upon the brain might also be interrupted by the constant digital use and the immersion in the digital world.

About the proliferative new development of digital psychiatric management in recent decades, there have already been various kinds of digitalised systems of healthcare delivery, digitalised information processing and storage, digital monitoring tools and charts for individual's instantaneous mental state, online consultations and standardised assessments, readily accessible information on psychiatric disorders and psychotropics in the internet, computer-based psychotherapeutic interventions like Cognitive Behavioural Therapy (CBT), digital drug ingestion tracking system, as well as GPS tracking for those patients at risk.

Regarding the further psychiatric research in our mind and brain and related disease in the Age of Digitalisation, it is being made further possible by the rapid development of digital tools like Functional MRI and different kinds of brain-mapping.

When it comes to the specific treatments in Psychiatry, the progressive advancement of therapeutic interventions in the brain, including Trans-cranial Magnetic Stimulation (TMS) and Deep Brain Stimulation (DBS), would not have been possible without the technological advancement brought about by digitalisation and AI.

As compared with these different aforementioned issues, the controversies in Psychiatry in the Age of Digitalisation can be even more intricate. Among them, the clinical data and human right issues in Psychiatry are becoming progressively complicated and sensitive in our daily practice in the Age of digitalisation, in a background of various issues of stigmatisation, accessibility and vulnerability. Further ethical considerations would definitely need more in-depth contemplation and deliberation, in order to protect our potentially vulnerable patients.

More ultimately, the essential and indispensable elements of human touch, empathy, transference and counter-transference in daily psychiatric practice in Psychiatry can be seriously jeopardised if there would be indiscriminate digitalisation.

DISCUSSION

On one hand, it is getting more and more clear that the progression of digitalisation is inevitable in human history.

On the other hand, it is getting more and more necessary for Psychiatry to progress further and leap higher, in order to face the present and future challenges towards the mind of the mankind, a major one of which would definitely be the projected estimation of depression as the most important cause of global disease burden in 2030[10].

In the first glance to everyone, digitalisation and AI appear irresistible as a quick, timely and easy solution to the challenges of our time, before the related harms and threats are becoming more and more conspicuous subsequently.

The stakeholders in the facing the upcoming upheavals would be patients, doctors, information technology (IT) and healthcare business entrepreneurs, service providers, scientists, researchers and governments.

It would be an unstoppable pendulum of struggle and consensus and struggle in due course.

Among these stakeholders, needless to say, the individual and collective interests of patients should always be given the utmost priority. In this regard, psychiatrists should continue to play an indispensable role to maximise the benefits, minimise the harms, improve well-being and safeguard the safety of our potentially vulnerable patients.

CONCLUSION

As a specialty in Medicine which is about the human inner experience as well as individual and collective meaning, the Age of Digitalisation is actually bringing more fundamental changes in Psychiatry than it had been anticipated.

That might even be a high time we revisited even more ontological issues, like mental health in the Age of Digitalisation.

With the potential and unprecedented impacts at different levels brought about by digitalisation and AI, we psychiatrists should constantly gate keep and review the drastic development of Psychiatry, not only from the medical perspective but also from inter-disciplinary perspectives of philosophy, culture and history, which would be a beacon to shed light on our misty way ahead.

In particular, conceptually and practically, digitalisation and AI should always be regarded and perused as an invented tool to assist us humans to improvise and personalise our psychiatric service to meet the ever-increasing psychiatric healthcare need now and in future, instead of as a substitute of us.

That comes to the need for advocacy of psychiatrists working with AI-assisted Psychiatry.

More important still, in this on-going, dynamic and multi-level processes of digitalisation of Psychiatry after the Millennium, human touch, empathy, humanity, and the boundary between human and AI should never be compromised.

In the end, with our concerted and pro-active efforts, I believe eventually these important and fundamental qualities of human beings would be filtered and retained across time and space, despite the imminent and unprecedented transformation in Psychiatry into the future world.

After all, Psychiatry is about experience and meaning, which makes us human.

P.S. At the time of writing this article, I read in the news that artificial neurones had been already invented as 'brain chips' with the potential to repair our brain, like in Alzheimer Disease. It is probably a matter of karma, initially beginning from the invention of AI by simulating to our neurones about one century ago to the subsequent invention by AI to replace our lost neurones in the Millennium, which is actually a beautiful interplay of digitalisation, AI and Psychiatry. This is also the time when humanity should come into play.

References

1. Marneros, A. Psychiatry's 200th Birthday. The British Journal of Psychiatry 2008; 193: 1-3.
2. Finger, S. (2010) Minds behind the Brain: A History of the Pioneers and their Discoveries. New York: Oxford University Press; 28-30.
3. Descartes, R. (1641) Meditations on First Philosophy, in The Philosophical Writings of René Descartes. Translated by Cottingham, J., Stoothoff, R. & Murdoch, D. in 1984. Cambridge: Cambridge University Press.
4. Freud, S. (1900) The interpretation of dreams. Translated by Strachey, J. Edited by Richards, A., Dickson, A. & Strachey, J. Middlesex: Penguin Books.
5. Freud, S. (1923) The Ego and Id. Translated by Strachey, J. Edited by Richards, A. Middlesex: Penguin Books.
6. Beavers, A. (2013). Alan Turing: Mathematical Mechanist. Alan Turing: His Work and Impact. Edited by Cooper, S. B. & van Leeuwen, J. Waltham: Elsevier. 481–485.
7. Frankish, K, Ramsey, WM. (Eds.). (2014). The Cambridge Handbook of Artificial Intelligence. UK, Cambridge University Press.
8. OyeBode, F. (2015). Sims' Symptoms in the Mind. Textbook of Descriptive Psychopathology. (5th ed.). Philadelphia: Saunders Elsevier.
9. Levitin, DJ. (2015). The Organized Mind: thinking straight in the age of information overload. UK, Penguin. 96.
10. Executive Board. 130th Session. Provisional agenda item 6.2. Global burden of mental disorders and the need for a comprehensive, coordinated response from health and social sectors at the country level. Report by the Secretariat. Geneva, World Health Organization (1 December 2011)

HONG KONG.
WHERE THE WORLD CHOOSES TO MEET.

With an exceptional spectrum of MICE's unique advantages and authentic experiences, this is where the world gets connected and inspired in every way. Hong Kong. The World's Meeting Place.

mehk | Meetings & Exhibitions Hong Kong

A division of Hong Kong Tourism Board

HONG KONG

CONNECT AND EXCEL

mehongkong.com

A Web-based Psychoeducation for Caregivers of Patients with First-episode Psychosis in Hong Kong and Possibility of Telepsychiatry

Dr Sherry KW CHAN

MBBS (HK), MRCPsych (UK), FHKCPsych, FHKAM (Psychiatry)

Specialist in Psychiatry
Clinical Assistant Professor, Department of Psychiatry, LKS Faculty of Medicine, The University of Hong Kong

Dr Sherry KW CHAN

INTRODUCTION

The role of caregivers of patients with psychosis is crucial at all stages of the illness. Support from caregivers helps to improve medication adherence and social functioning and to reduce hospitalisation duration for patients with psychosis.[1,2] However, this is often demanding to the caregivers, particularly during the initial phase of the illness. With very little understanding of psychosis, caregivers often feel shocked, frustrated and helpless when their relatives become unwell for the first time.[3,4] Therefore, caregivers often experience distress with a high rate of depression, anxiety and subjective sense of significant burden.[5] About one-third of the caregivers have been found to suffer from depression.[6] Therefore, support and psychoeducation of the caregivers of patients with the first episode of psychosis (FEP) would impact the outcome of patients and overall health of caregivers.[7]

Various international clinical guidelines (International Early Psychosis Association Writing Group, 2005) have suggested family intervention as one of the key psychosocial interventions. Studies have provided solid evidence on the effectiveness of a family-focused intervention on patients with FEP including a reduction in rate of relapse and hospitalisation, as well as an improvement in adherence and functional outcomes.[8,9] Psychoeducation, aiming to provide knowledge on psychosis, and to improve caregivers' communication skills and coping skills in caring for the patients, is one of the key components of the family-focused intervention. The effectiveness of the caregivers' psychoeducation on its own has been demonstrated.[8-13] The role of the family as an informal source of care for patients with psychosis is particularly significant in Hong Kong in view of the family-oriented Chinese culture, and as more than 80% of patients are living with their family of origin[14].

Despite the stated evidence on the effectiveness of the caregiver psychoeducation, implementation of these programmes in the real world has been challenging. Most of the programmes are in the form of short-term face-to-face family group intervention. The operation of this format is restricted by the high case-load of the healthcare professionals in Hong Kong and the low accessibility of the service. Furthermore, the caregiver stigma, multiple roles and responsibilities of caregivers and the lack of flexibility of the service have all restricted the participation of caregivers in programmes in its traditional face-to-face format. In view of the limitation, telepsychiatry has been suggested as a possible format in delivering psychoeducation to caregivers in Europe with demonstrable effectiveness in improving knowledge on the illness among the caregivers.[15] Within this context, internet-based psychoeducation programme for caregivers of psychosis (iPEP) (www.ipep.hk) was established in 2013, funded by the Health Care Promotion Found (HCPF) to fill the gaps in the relevant services in Hong Kong.

DEVELOPMENT OF iPEP 2013-2019

The internet-based psychosis education programme for caregivers (iPEP) was established in collaboration with several local non-governmental organisations (NGOs) with the aim to provide up-to-date online information about psychosis and available resources. The needs of users with a wide age range were taken into consideration during the process of development.[16] An example in point is the design of a simple operating interface. The content of iPEP comprises three components:

1) 34 short YouTube videos prepared and recorded by the healthcare professionals including psychiatrists, social workers and clinical psychologists ranging between 2 to 5 minutes each to provide detailed information about psychosis, such as aetiology of psychosis, different treatment modalities, recovery, relapse, side effects of medication, risk management and necessary skills as caregivers (Table 1). An article of the same content in PDF format is also available for downloading;

2) Compendium of local mental health services provided by both NGOs and the government, including services in hospitals, vocational training, residential care services and financial aids (17 articles) is provided as a one-stop resource centre; and

3) An interactive on-line forum to facilitate communication between the caregivers and healthcare professionals. Caregivers need to join as members of the website in order to access the forum, where they can post questions that would be answered by the professionals. Updated information will also be uploaded on the forum from time to time. Caregivers can also post questions directly to the website administrator through the 'Contact Us' function of the website. Response will be provided by the administrator or the healthcare team.

During the funding period (2013-2015) with active promotion, including public talks, there were 809

Table 1. Content and structure of iPEP website (Developed by author)

Psychosis knowledge

Basic knowledge	*Treatment*	*Recovery*
1. What is psychosis?	9. What are the treatments for psychosis?	15. What is recovery?
2. What are the symptoms?	10. How can medication help?	16. Can patients with psychosis go to school?
3. What is a hallucination?	11. How about treatments other than medication?	17. Can patients with psychosis go to work?
4. What is a delusion?	12. What are the uses and side effects of the medication?	18. What are the risk factors for relapse?
5. What are the negative symptoms?	13. How can side effects be managed?	19. How can relapse be prevented?
6. What are the stages of psychosis?	14. Can I stop medications on my own?	
7. How is psychosis being diagnosed?		
8. What causes psychosis?		

Caregiver support

Tips on caring for patients	*Caregivers' self-support*
1. Why is family support important?	10. What might be caregiver be feeling?
2. Suggested skills and attitude towards patients with psychosis?	11. What expectations should I have?
3. Should I look after the patient long-term?	12. Am I stressed?
4. What should I do if the patient is reluctant to see the doctor or take medications?	13. How can I relax myself?
5. What should we do when the patient is experiencing delusions or hallucinations?	14. How should I express praise and care?
6. What should I do if the patient lacks motivation?	15. How should I express discontent?
7. What should we do if the patient is suicidal?	
8. What should we do if the patient attempts to harm other people?	
9. What are the procedures for involuntary admission?	

caregivers registered as iPEP members with a monthly average page view count of 3204 based on Google analytics (http://www.google.com/analytics/). Evaluation of the members' experience of the use of iPEP has been conducted and revealed 85.2% of member caregivers subjectively agreed that the website improved their knowledge on psychosis; over 80% of them would recommend the website to others.[17] After the funding ended in 2015, there are no further active promotion and publicity about the iPEP. However, the number of iPEP members has further increased to 939 with a cumulative pageview of 606,566 based on Google analytics at the end of 2019. Caregivers may get to know the website either via recommendation by others including healthcare providers or via their own online search. This feedback suggested that there is a need for comprehensive online resources for the caregivers. A total of 98 questions have been posted by the caregivers through the forum and the 'Contact Us' function over the last six years; most often-asked questions are medication-related, both of which suggest that there is a need for an anonymous online consultation platform for the caregivers.

FUTURE DEVELOPMENT OF iPEP AND POTENTIAL OF TELEPSYCHIATRY

Telepsychiatry is the use of communication technologies to provide psychiatric services from a distance and has been around for half a century. One of the main formats has been the videoconferencing-based telepsychiatry, which has enabled and empowered service delivery to achieve equality of access, and which is particularly useful for rural population. There is supportive evidence for the effectiveness of such telepsychiatry.[18] However, this service may not be readily applicable in Hong Kong because the city carries a high population density and effective public transport system. More recently, there has been active development in using artificial intelligence to assist mental health diagnosis and service delivery, such as the chatbots, which allows for anonymity and accessibility. Although the effectiveness of using chatbots to assist the diagnosis of mental health disorders is still at its embryonic stage,[19] its usage in providing health-related information in physical conditions[20] and in delivering positive psychology[21] has yielded some positive outcomes. The experience of iPEP suggested that there is a need for providing information about mental health illness and lending support to the caregivers online. This iPEP platform could form the basis for the future development of chatbots service for caregivers of psychosis and other mental health patients in Hong Kong.

CONCLUSION

There is a service gap in psychoeducation and in support to caregivers of patients with psychosis. The development of iPEP and its usage over the last six years have suggested that an online information resource and communication platform between caregivers and healthcare professionals could be a possible approach to fill the gaps of existing service. Our experience gathered from iPEP could pave the way for the future development of chatbots service for caregivers of patients with psychosis and other mental health. However, the integration of such services with the existing mental health service would be crucial for a comprehensive and cost-effective multidisciplinary service for patients with psychosis and other mental health conditions.

References

1. Penn, D. L., Waldheter, E. J., Perkins, D. O., et al., Psychosocial treatment for first-episode psychosis: a research update. Am. J. Psychiatry 2005;162(12): 2220-2220
2. Sin, J., Moone, N., and Wellman, N., Developing services for the carers of young adults with early-onset psychosis–listening to their experiences and needs. J. Psychiatr. Ment Health Nurs 2005; 12(5): 589-597
3. Addington, J. and Burnett, P. Working with families in the early stages of psychosis. Psychological interventions in early psychosis. Psychological intervention in early psychosis. A treatment handbook 2004; 99-116
4. Mui, EYW., Chan SKW., Chan, PY., et al., Systematic review (meta-aggregation) of qualitative studies on the experiences of family members for individuals with early psychosis. Int Rev Psychiatry. 2019; (5-6):491-509.doi:10.1080/09540261.2019.1659236
5. Martens, L., and Addington, J. The psychological well-being of family members of individuals with schizophrenia. Soc. Psychiatry Psychiatr. Epidemiol. 2001; 36(3): 128-133

6. Kuipers, E., and Raune, D., The early development of expressed emotion and burden in the families of first-onset psychosis. Early Intervention in Psychosis Wiley 2000 pp.128-140. Birchwood, M., Jackson, M. and Fowler, D. Editors
7. Addington, J., Collins, A., McCleery, A., et al. The role of family work in early psychosis. Schizophr. Res. 2005; 79(1): 77-83
8. Pharoah, F., Mari, J., Rathbone, J., Family intervention for schizophrenia. The Cochrane Collaboration Review, 2010; 1-159
9. Mari, J., De, J., and Streiner, D. An overview of family interventions and relapse on schizophrenia: meta-analysis of research findings. Psychol. Med 1994; 24: 565-565
10. Barbato, A., and D'Avanzo, B. Family interventions in schizophrenia and related disorders: a critical review of clinical trials. Acta Psychiatr Scand, 2000; 102: 81-97
11. Jewell, T. C., Downing, D., and McFarlane, W. R. Partnering with families: multiple family group psychoeducation for schizophrenia. J. Clin. Psychol. 2009; 65: 868-878
12. Lucksted, A., McFarlane, W., Downing, D., et al., Recent developments in family psychoeducation as an evidence-based practice. J. Marital Fam. Ther. 2012; 38:101-121
13. Rummel-Kluge, C., and Kissling, W., Psychoeducation in schizophrenia: new developments and approaches in the field. Curr. Opin. Psychiatry 2008; 21: 168-172
14. Chan, S.K., So, H.C., Hui, C.L., et al., 10-year outcome study of an early intervention program for psychosis compared with standard care service. Psychol. Med. 2015; 45(6): 1181-1193. doi: 10.1017/S0033291714002220
15. Haley, C., O'Callaghan, E., Hill, S., et al. Telepsychiatry and carer education for schizophrenia. Eur. Psychiatry. 2011; 26(5): 302-304. doi: 10.1016/j.eurpsy.2009.12.021
16. Rotondi, A.J., Sinkule, J., Haas, G.L., et al., Designing websites for persons with cognitive deficits: Design and usability of a psychoeducational intervention for persons with severe mental illness. Psychol Serv. 2007; 4(3): 202-224
17. Chan, SK., Tse S., Sit HL., et al., Web-Based Psychoeducation Program for Caregivers of First-Episode of Psychosis: An Experience of Chinese Population in Hong Kong. Front Psychol. 2016; 7:2006. doi: 10.3389/fpsyg.2016.02006
18. Chakrabarti, Subho. "Usefulness of Telepsychiatry: A Critical Evaluation of Videoconferencing-Based Approaches." World Journal of Psychiatry 2015; 5 (3): 286–304
19. Jungmann, Stefanie Maria, Timo Klan, et al., "Accuracy of a Chatbot (Ada) in the Diagnosis of Mental Disorders: Comparative Case Study With Lay and Expert Users." JMIR Formative Research 2019; 3 (4): e13863
20. Bibault, Jean-Emmanuel, Benjamin Chaix,. "A Chatbot Versus Physicians to Provide Information for Patients With Breast Cancer: Blind, Randomized Controlled Noninferiority Trial." Journal of Medical Internet Research 2019; 21 (11): e15787
21. Greer, Stephanie, Danielle Ramo, et al. "Use of the Chatbot 'Vivibot' to Deliver Positive Psychology Skills and Promote Well-Being Among Young People After Cancer Treatment: Randomized Controlled Feasibility Trial." JMIR mHealth and uHealth 2019; 7 (10): e15018

Time to Enhance Our Preparedness to Handle Trauma and Stress-related Disorders in Hong Kong

Dr Ivan WC MAK

MBChB (HK), MRCPsych (UK), FHKCPsych, FHKAM (Psychiatry), DCPsyc RCP&S (Irel), MSc (Epidemiology and Biostatistics; CUHK), GradDipFamMed (Monash)

Specialist in Psychiatry

Dr Ivan WC MAK

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 March 2020.

INTRODUCTION

Traumatic man-made incidents and natural disasters can occur at any time in life, possibly resulting in post-traumatic stress disorder (PTSD), the onset and persistence of which tends to vary by trauma type, *e.g.* war, violence, an accident, or the death (or witnessing death) of a loved one.[1] Furthermore, about half of PTSD patients have also been diagnosed with major depressive disorder.[2] This article provides some clinical insights on the effective management of PTSD in the Hong Kong context and discusses the latest developments in scientific research as well as international guideline recommendations. Also, in view of the recent social unrest and encompassing psychiatric burden, it is hoped that this article will increase the awareness and preparedness of mental health professionals in handling related PTSD incidents.

TRAUMAS AND PTSD

In the World Health Organisation World Mental Health (WMH) Surveys that were conducted in 24 countries (2001-2012;[3] n = 68,894), 70.4% of respondents had experienced lifetime traumas, at an average of 3.2 traumas per respondent.[1] While disaster-related PTSD is relatively uncommon in high-income countries, it is worth noting that disasters caused by humans were associated with significantly higher odds of PTSD vs natural disasters (OR = 3.3, 95% CI: 1.1–9.7).[4] In Hong Kong, preliminary findings of the Hong Kong Mental Morbidity Survey (2010-2013) reported that 65% of 4,644 adult participants had a traumatic experience, which was associated with higher Trauma Screening Questionnaire (TSQ) scores, higher psychological distress, lower social support, and lower life-functioning.[5] Previous studies of the 2003 severe acute respiratory syndrome (SARS) epidemic showed that the cumulative prevalence of any psychiatric disorder among survivors was as high as 58.9%, and remained at 33.3% at 30 months; for PTSD, the prevalence was 25.6% in this group.[6]

As our understanding of PTSD continues to evolve, the American Psychiatric Association has made several changes to the classification of PTSD in the 5th Edition of *The Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; published in 2013). Notable changes include:

i) the creation of a new diagnostic category named "Trauma and Stressor-related Disorders", which removes PTSD from the anxiety disorders category, indicating that PTSD is distinct in character from other anxiety disorders;

ii) in Criterion A:
emotional reactions to the traumatic event (*e.g.* fear, helplessness, horror) are no longer a part of the criterion because it is noted that the emotional presentation of an individual varies. The definition of a traumatic event was further refined: stressful events without immediate threat to life or physical injury (*e.g.* divorce or job loss) are excluded, and medically-based trauma was limited to sudden catastrophe, which excludes non-immediate illnesses (*e.g.* terminal cancer) and medical incidents involving natural causes (*e.g.* heart attack). A fourth exposure type (A4) was added, which involves repeated or extreme exposure to aversive details of a traumatic event,[7] which applies to work-related exposure as part of professional responsibilities (*e.g.* military mortuary services or child abuse investigations), but not to exposure through the mass media. Specifically, criterion A4 "does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work-related,"[8] likely because of a lack of direct association between exposure to media reports, which is highly common in the society, and PTSD.

iii) An increase in the number of symptom groups from three to four: in addition to experiencing, avoidance and arousal, the group of negative cognitions and mood were added. Negative cognitions and mood represent myriad feelings, from a persistent and distorted sense of blame of self or others to estrangement from others or markedly diminished interest in activities, to an inability to remember key aspects of the event. The addition emphasises the important correlation of negative affective conditions with PTSD.[7,8]

CHANGE TO INTERNATIONAL CLASSIFICATION OF DISEASES ICD-11

Acute stress is a brief experience of intense psychological distress that follows exposure to a traumatic event. Whereas the DSM-5 continues to classify acute stress as a mental disorder (i.e. Acute Stress Disorder), the *International Classification of Diseases ICD-11*, which was released in June 2018 and will come

into effect on January 1, 2022,[9] has removed acute stress from the mental disorders section. The ICD-11 reclassified acute stress as a reaction to trauma and placed it in a section on factors influencing health. The intention is to recognise a non-pathological category of transient emotional, cognitive, behavioural and somatic reactions in response to trauma. Besides narrowing the definition of PTSD, the *ICD*-11 created a new complex PTSD category that comprises of six symptom clusters: they include not only the three clusters of experiencing, avoidance and arousal, but also difficulties in emotion regulation, problems with self-concept such as feelings of shame, guilt or failure, and disturbances in interpersonal relationship functioning.[10] This new PTSD category describes the disturbance in self-organisation that may result from multiple, chronic or repeated traumas.[11] The classification helps to distinguish patients whose conditions are focused on the trauma itself from those who experience extensive difficulties throughout their lives.

PSYCHOLOGICAL MANAGEMENT

Traumatic memory is a key concept in understanding the development of PTSD. Human beings have the ability to acquire, store and retrieve information, which helps our survival. Further, remembering fearful events may prime us to react more quickly to similar threats if they happen again. PTSD arises when the retention of fearful memories become extreme and persistent, which usually results from exposure to a traumatic event. Some authors suggested that the time between the traumatic event and the manifestation of PTSD are "golden hours", during which memory of the trauma consolidates and spontaneous recovery takes place.[12] The concept of golden hours is well-accepted in other areas of medicine, including, most famously, in cerebrovascular accidents where the administration of a thrombolytic agent is highly effective if given within the first three hours from the accident occurrence, but may otherwise be ineffective or even harmful. Applying an analogous concept of golden hours to PTSD provides some novel treatment insights. Interventions during these golden hours are aimed at preventing traumatic memory consolidation (*i.e.* secondary prevention) and not to deter spontaneous recovery.[12]

It is important to observe the patient during the first month after the occurrence of trauma before confirming the diagnosis and beginning treatment; such observation is termed *watchful waiting* or active monitoring. The United Kingdom's National Institute for Health and Care Excellence (NICE) 2018 guideline recommends considering active monitoring within one month of a traumatic event (1.6.4 and 1.6.6).[13]

Of note, the NICE guideline (1.6.5) specifically discourages the use of *psychologically focused debriefing* for the prevention or treatment of PTSD.[13] After the September 11, 2001, terrorist attacks on New York City, thousands of counsellors provided immediate debriefing services to survivors, which typically involved encouraging survivors to express their cognitive and emotional reactions, in addition to other advice and referral components.[14] However, various studies generally showed that traumatised individuals who received psychological debriefing were doing significantly worse than those who did not, even years after the traumatic incidents.[15] The process of debriefing may refresh and enhance the memory of the trauma and prevent spontaneous recovery from reducing it.[15] Further, debriefing in group sessions may cause *secondary traumatisation* to the participants, where the emotional experiences of listening, understanding and caring for those who are traumatised can become a stressor.[16]

In recent years, the recommended practices during watchful waiting have shifted away from psychological debriefing toward *psychological first aid* (PFA).[17,18] PFA aims to provide "basic, non-intrusive pragmatic care with a focus on listening but not forcing talk, assessing needs and concerns, ensuring that basic needs are met, encouraging social support from significant others and protecting from further harm."[19] Table 1 lists some of the basic components of PFA.

Table 1. Basic components of psychological first aid. (Adapted from "Psychological first aid: Guide for field workers © World Health Organization 2011")

	Component
a.	Contact and engagement
b.	Safety and comfort
c.	Protection from further harm and distress
d.	Practical assistance
e.	Reunion with family and loved ones (in person or by video/ telephone)
f.	Openness for sharing (but not forced)
g.	Information on coping
h.	Information or linkage with collaborative services

For prevention of PTSD, besides watchful waiting/ active monitoring, NICE also recommended individual *trauma-focused cognitive behavioural therapy* (TF-CBT) intervention to children, young people and adult who have clinical important symptoms of PTSD and have been exposed to trauma within the last month (1.6.6, 1.6.15). The core elements of TF-CBT include psychoeducation, coping strategies, gradual exposure, cognitive processing and caregiver participation, and robust study findings have supported its effectiveness.[20]

For the treatment of PTSD for children, young people and adult, *i.e.* those who have clinical important symptoms of PTSD who have presented more than one month after a traumatic event, NICE-recommended psychological interventions include TF-CBT (1.6.15-16) and *eye movement desensitisation and reprocessing* (EMDR; 1.6.18-19).[13] In EMDR, re-exposure is combined with eye movements to allow for emotional processing of the patient's excessively negative appraisals of the trauma.[14] Results from a 2018 meta-analysis of 14 randomised controlled trials (RCTs) suggested that EMDR is better than CBT in reducing post-traumatic symptoms (p = 0.006; 11 studies) and anxiety (p = 0.005; 5 studies), but not depression (p = 0.08; 8 studies).[21] Another meta-analysis of 11 RCTs suggested that EMDR may be more suitable than CBT for PTSD patients with prominent intrusion or arousal symptoms, while noting that the included studies were limited in both quantity and quality.[22] While awaiting for further comparison

studies, clinical applicability shall depend on the availability of proper training and expertise in these treatment areas.

Pharmacotherapy

In clinical practice, avoidance is commonly present among PTSD patients. Some patients decline or resist psychological therapy because it may touch on the traumatic experience, and prefer medication instead, especially when initiating treatment. For medication treatment, the NICE, American Psychological Association, and Maudsley guidelines generally recommend using selective serotonin reuptake inhibitor (SSRI) antidepressants (*e.g.* sertraline, fluoxetine or paroxetine) or the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine (modified release).[13,23,24] These are usually given at a lower starting dose than when indicated for major depressive disorder (MDD). Patients who are resistant to SSRIs may be given mirtazapine,[23] which also has a sedative effect to help with sleep. Anti-psychotics such as risperidone, which may help with flashbacks and nightmares (but are less helpful with avoidance and hyperarousal symptoms of PTSD),[13,23] could be given at a very low dose.

However, benzodiazepines do not appear to be effective for sleep disturbances in PTSD,[13] and some authors suggest that medication-induced deep sleep might interfere with the natural processing and extinction of traumatic memory.[25] A 2016 meta-analysis of 6 RCTs suggested that the α-1-adrenergic receptor blocker prazosin produced moderate to large effects in reducing overall PTSD symptoms and nightmares, but similar results were not reproduced in a 2018 study with veterans (n = 304) vs placebo.[26] The APA guideline also noted that the strength of evidence for prazosin in overall PTSD symptom reduction or remission is insufficient.[24] Rat models and exploratory studies suggested that the β-adrenergic receptor antagonist propranolol may help to block traumatic memory reconsolidation, which will require further studies to support any clinical applications.[27]

Note that due to the scarcity of evidence of an effect, the NICE guideline recommends against the use of drugs to: i) treat PTSD in children and young people aged < 18 years (1.6.14); and ii) prevent PTSD (1.6.24).

PTSD and Depression

The aetiology of PTSD and depression may be complex and interlinked: for example, a combination of high negative affect and low extraversion may constitute a pre-existing trait that confers vulnerability toward comorbid PTSD and MDD.[2] Clinically, it is often difficult to differentiate PTSD from depression. While PTSD patients are often in a depressive mood, they may also have the depressive disorder as a comorbid condition. Statistically, while MDD is prevalent in about 50% of PTSD patients, it is not the case vice versa: a study of 1,346 MDD patients found that only 1.5% had comorbid PTSD.[28] For differential diagnosis, the physician may observe the extent and severity of depression in the patient. For example, for a patient with comorbid depressive disorder, the experience of depression would tend to manifest outside of the traumatic experience, such as feeling useless or that survival is meaningless.

Studies on treatment for PTSD with co-existing depression are lacking. The NICE guideline recommends taking caution to treat the depression first if it is highly symptomatic or the patient poses a risk of self-harm (1.7.1).[13] However, hypothetically, since the traumatic experience would likely aggravate the depressive mood, treating the PTSD first should help to alleviate the depression, too. Augmentation of antidepressant pharmacotherapy with low-potency antipsychotics have been documented in the literature, but cannot be regarded as evidence-based.[28] Some preliminary data suggest that for PTSD patients with depression, trauma-focused interventions that include targeting comorbid depression may enhance intervention effectiveness and reduce dropouts.[2,29]

Psychophysiological, neuroimaging, endocrinological and molecular genetic studies have identified biological markers for PTSD.[30] For example, when compared with both healthy and trauma-exposed controls, PTSD patients demonstrated decreased grey matter volume within the subcortical (including the hippocampus and amygdala) and cortical brain regions.[31] Decreased cortisol levels may also be observed, caused by "shutting-down" of the hypothalamic-pituitary-adrenal cortical (HPA) axis from negative feedback.[30] Some studies suggested that antidepressant treatment may help reverse the stress-induced atrophy and promote neurogenesis of hippocampus.[32]

CARING FOR HONG KONG PATIENTS

Traditionally, Hong Kong is regarded as one of the safest cities in the world,[33] with low rates of homicides and disasters.[34] Nevertheless, disasters may happen from time to time, such as the 2003 severe acute respiratory syndrome (SARS) epidemic, or the 2018 typhoon Mangkhut. Social unrests emerged in recent years, including the 2014 Occupy Central movement, 2016 Mongkok violence and the 2019 anti-Extradition Bill protests.

The Hong Kong FAMILY Cohort study reported that the prevalence of probable depression increased from 1.3% in 2011-2014 (n = 17,002) to 5.3% during the Occupy Central protests in 2014 and 9.1% in June-July 2019 (n = 1,269).[35] Due to the extensive (active and passive) public involvement of the 2019 protests, citizens may have been exposed to potentially traumatic incidents in the form of threatened deaths, serious injuries, violence and/or related damages. The incidence of trauma- and stress-related disorders (and possibly some secondary traumatisation) would be expected to rise significantly.

During the 2013 civil unrest in Turkey, among 296 enrolled patients who sustained injuries from riot control and/or related exposure, 117 were psychiatrically evaluated, and 43% were diagnosed with acute stress disorder, including some with subsequent PTSD and/or MDD.[36] In the U.S., a survey of community members and police officers (n = 565) who were exposed

to violence in the 2014 Ferguson, Missouri protests reported a high level of distress overall, and all assessed aspects of proximity to the violence (*e.g.* media, life interruption, and fear) were associated with mental health outcomes.[37] When traumatic incidents occur, the uncertainties (for both patients and care professionals) and associated risks (*e.g.* to the patient's loved ones) can also impose a heavy psychological burden on the society, with long-lasting effects.[6] Consistent, protocol-based screening and referral of trauma patients could help to identify those who are at risk, allowing for the provision of timely monitoring and treatment if necessary.[38]

Trauma can produce intimate, practical consequences and psychological effects on one's daily life. It is a common misconception that traumatic memories may be easily forgotten or even denied; on the contrary, PTSD patients often find it extremely difficult to forget these memories. For example, while SARS survivors were cured of the acute viral infection, in a ten-year follow-up study of a cohort of SARS survivors treated in the United Christian Hospital in Hong Kong with overall response rate of 69.3%, nearly one fifth (19.7%) still suffered from PTSD, followed by depressive disorder (14.7%) and panic disorder (4.9%). (unpublished data). Contrary to what one might wishfully expect of a "speedy recovery" from trauma, PTSD can be a long-term condition.[39] In this regard, the physician must be extra-prudent in handling the patient's memory of the traumatic incident, to maintain a trusting patient-physician relationship and to effectively manage this complex condition.

It is hoped that this article may help to increase the awareness and preparedness of mental health professionals in handling PTSD cases. Special attention should be paid to the delicate and long-lasting nature of the condition, the need for watchful waiting, and the various recent developments in psychological and pharmacological management as discussed above. Voluntary screening and referrals of those who experienced trauma during the recent protests may facilitate case identification. As such, the foreseeable long-term psychiatric damages may be reduced.

References

1. Kessler RC., Aguilar-Gaxiola S., Alonso J., et al. Trauma and PTSD in the WHO World Mental Health Surveys. Eur J Psychotraumatol. 2017; 8(sup5): 1353383
2. Flory JD. & Yehuda R. Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. Dialogues Clin Neurosci. 2015; 17(2): 141-150
3. Kessler RC., Heeringa SG., Pennell B-E., et al. 3 - Methods of the World Mental Health Surveys. In: Scott KM, de Jonge P, Stein DJ, Kessler RC, eds. Mental Disorders Around the World - Facts and Figures from the WHO World Mental Health Surveys. Cambridge University Press; 2018: 9-40
4. Bromet EJ., Atwoli L., Kawakami N., et al. Post-traumatic stress disorder associated with natural and human-made disasters in the World Mental Health Surveys. Psychol Med. 2017; 47(2): 227-241
5. Wu KK. PTSD and loss: preliminary findings from a territory-wide epidemiology study in Hong Kong. Eur J Psychotraumatol. 2014; 5: 26517
6. Mak IW., Chu CM., Pan PC., et al. Long-term psychiatric morbidities among SARS survivors. Gen Hosp Psychiatry. 2009; 31(4): 318-326
7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. American Psychiatric Association Publishing; 2013
8. Pai A., Suris AM., North CS. Posttraumatic Stress Disorder in the DSM-5: Controversy, Change, and Conceptual Considerations. Behav Sci (Basel). 2017;7(1)
9. WHO releases new International Classification of Diseases (ICD 11) [press release]. Geneva, Jun 18, 2018
10. Maercker A., Brewin CR., Bryant RA., et al. Diagnosis and classification of disorders specifically associated with stress: proposals for ICD-11. World Psychiatry. 2013; 12(3): 198-206
11. Brewin CR., Cloitre M., Hyland P., et al. A review of current evidence regarding the ICD-11 proposals for diagnosing PTSD and complex PTSD. Clin Psychol Rev. 2017; 58: 1-15
12. Carmi L., Fostick L., Burshtein S., et al. PTSD treatment in light of DSM-5 and the "golden hours" concept. CNS Spectr. 2016; 21(4): 279-282
13. National Institute for Health and Care Excellence (UK). Post-traumatic Stress Disorder - NICE Guideline. 2018. Available at: nice.org.uk/guidance/ng116
14. Foa EB., Gillihan SJ., Bryant RA. Challenges and Successes in Dissemination of Evidence-Based Treatments for Posttraumatic Stress: Lessons Learned From Prolonged Exposure Therapy for PTSD. Psychol Sci Public Interest. 2013; 14(2): 65-111
15. Zohar J., Juven-Wetzler A., Sonnino R., et al. New insights into secondary prevention in post-traumatic stress disorder. Dialogues Clin Neurosci. 2011; 13(3): 301-309
16. Mordeno IG., Go GP., Yangson-Serondo A. Examining the dimensional structure models of secondary traumatic stress based on DSM-5 symptoms. Asian J Psychiatr. 2017; 25: 154-160
17. Pandya A. A review and retrospective analysis of mental health services provided after the September 11 attacks. Can J Psychiatry. 2013; 58(3): 128-134
18. World Health Organization, War Trauma Foundation, World Vision International. Psychological first aid: Guide for field workers. Geneva: WHO; 2011
19. World Health Organization. Guidelines for the Management of Conditions Specifically Related to Stress. Geneva: WHO; 2013
20. de Arellano MA., Lyman DR., Jobe-Shields L., et al. Trauma-focused cognitive-behavioral therapy for children and adolescents: assessing the evidence. Psychiatr Serv. 2014; 65(5): 591-602
21. Khan AM., Dar S., Ahmed R., et al. Cognitive Behavioral Therapy versus Eye Movement Desensitization and Reprocessing in Patients with Post-traumatic Stress Disorder: Systematic Review and Meta-analysis of Randomized Clinical Trials. Cureus. 2018; 10(9): e3250
22. Chen L., Zhang G., Hu M., et al. Eye movement desensitization and reprocessing versus cognitive-behavioral therapy for adult posttraumatic stress disorder: systematic review and meta-analysis. J Nerv Ment Dis. 2015; 203(6): 443-451
23. Taylor DM., Barnes TRE., Young AH. The Maudsley Prescribing Guidelines in Psychiatry, 13th Edition. Wiley-Blackwell; 2018
24. Guideline Development Panel for the Treatment of PTSD in Adults. Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults. American Psychological Association; 2017
25. Lipinska G., Baldwin DS., Thomas KG. Pharmacology for sleep disturbance in PTSD. Hum Psychopharmacol. 2016; 31(2): 156-163
26. Stein MB. Pharmacotherapy for posttraumatic stress disorder in adults. In: Roy-Byrne PP, Hermann R, eds. UpToDate. Waltham, MA: UpToDate. (Accessed Jul 17, 2019)
27. Shad MU., Suris AM., North CS. Novel combination strategy to optimize treatment for PTSD. Hum Psychopharmacol. 2011; 26(1): 4-11
28. Dold M., Bartova L., Kautzky A., et al. The impact of comorbid post-traumatic stress disorder in patients with major depressive disorder on clinical features, pharmacological treatment strategies, and treatment outcomes - Results from a cross-sectional European multicenter study. Eur Neuropsychopharmacol. 2017; 27(7): 625-632
29. Nixon RD., Nearmy DM.. Treatment of comorbid posttraumatic stress disorder and major depressive disorder: a pilot study. J Trauma Stress. 2011; 24(4): 451-455
30. Pitman RK., Rasmusson AM., Koenen KC., et al. Biological studies of post-traumatic stress disorder. Nat Rev Neurosci. 2012; 13(11): 769-787
31. O'Doherty DCM., Tickell A., Ryder W., et al. Frontal and subcortical grey matter reductions in PTSD. Psychiatry Res Neuroimaging. 2017; 266: 1-9
32. Bremner JD., Elzinga B., Schmahl C., et al. Structural and functional plasticity of the human brain in posttraumatic stress disorder. Prog Brain Res. 2008; 167: 171-186
33. The Economist - Intelligence Unit. Safe Cities Index 2019. https://www.nec.com/en/global/ad/safecitiesindex2019/index.html. Accessed Nov 28, 2019
34. Lam RPK., Leung LP., Balsari S., et al. Urban disaster preparedness of Hong Kong residents: A territory-wide survey. International Journal of Disaster Risk Reduction. 2017; 23: 62-69
35. HKUMed reports real-time population data on depression and suicidal ideation: a ten-year prospective cohort [press release]. The University of Hong Kong, Jul 11, 2019
36. Unuvar U., Yilmaz D., Ozyildirim I., et al. Usage of Riot Control Agents and other methods resulting in physical and psychological injuries sustained during civil unrest in Turkey in 2013. J Forensic Leg Med. 2017; 45: 47-52
37. Galovski TE., Peterson ZD., Beagley MC., et al. Exposure to Violence During Ferguson Protests: Mental Health Effects for Law Enforcement and Community Members. J Trauma Stress. 2016; 29(4): 283-292
38. Bolduc A., Hwang B., Hogan C., et al. Identification and Referral of Patients at Risk for Post-traumatic Stress Disorder: A Literature Review and Retrospective Analysis. Am Surg. 2015; 81(9): 904-908
39. Marmar CR., Schlenger W., Henn-Haase C., et al. Course of Posttraumatic Stress Disorder 40 Years After the Vietnam War: Findings From the National Vietnam Veterans Longitudinal Study. JAMA Psychiatry. 2015; 72(9): 875-881

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Time to Enhance Our Preparedness to Handle Trauma and Stress-related Disorders in Hong Kong" by Dr Ivan WC MAK and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 March 2020 Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. Natural disasters were found to be associated with a significantly higher risk of development of post-traumatic stress disorder (PTSD) compared to disasters caused by humans.
2. In the 5th Edition of The Diagnostic and Statistical Manual of Mental Disorder (DSM-5), PTSD is indicated as being distinct in character from other anxiety disorders.
3. In the 11th Edition of International Classification of Disease (ICD-11), difficulties in emotion regulation, problems with self-concept, and disturbances in interpersonal relationship functioning are included as new clusters of symptoms.
4. The process of debriefing is strongly recommended for all survivors of traumatic events with proven evidence in significantly reducing the risk of subsequent development of PTSD.
5. The practice of psychological first aid (PFA) during the watchful waiting period is considered being "old-fashioned" and is not recommended in recent years.
6. When using antidepressant in the treatment of PTSD, a lower starting dose than for treating the major depressive disorder is recommended.
7. Benzodiazepines are found to be effective and beneficial for treating sleep disturbances in PTSD.
8. The UK National Institute for Health and Care Excellence (NICE) guideline does not recommend the use of medications to prevent the development of PTSD.
9. Patients with PTSD are found to have decreased grey matter volume within the subcortical and cortical brain region.
10. In a ten-year follow-up study of SARS patients in Hong Kong, only less than ten percent of them were still found to be suffering from PTSD.

ANSWER SHEET FOR MARCH 2020

Please return the completed answer sheet to the Federation Secretariat on or before 31 March 2020 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Time to Enhance Our Preparedness to Handle Trauma and Stress-related Disorders in Hong Kong

Dr Ivan WC MAK

MBChB (HK), MRCPsych (UK), FHKCPsych, FHKAM (Psychiatry), DCPsyc RCP&S (Irel), MSc (Epidemiology and Biostatistics; CUHK), GradDipFamMed (Monash)

Specialist in Psychiatry

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to February 2020 Issue

Cosmetic Upper Eyelid Surgery

1. T **2.** F **3.** F **4.** T **5.** T **6.** T **7.** T **8.** F **9.** T **10.** F

Timely ADHD Management Makes A Difference!

BIPOLAR DISORDER

As High as 21% of Patients Have Comorbid ADHD[1]

Comorbid ADHD Hastens an Earlier Onset of BD[3]

Comorbid ADHD Escalates Disease Burden of MDD[2]

DEPRESSION

Up to 16% Patients Have Comorbid ADHD[4]

CONCERTA® Improved All QoL Indexes[5]

CONCERTA® Reduced ADHD Symptoms as Early as Week 2[6]

2 Weeks

Individualised Dose Regimen with Demonstrated Efficacy[6]

CONCERTA® - First-line Recommendation in ADHD Practice Guidelines[7,8]

CADDRA
CANADIAN ADHD RESOURCE ALLIANCE

NICE
National Institute for Health and Care Excellence

ADHD: attention deficit hyperactivity disorder; BD: bipolar disorder; MDD: major depressive disorder; QoL: quality of life.

References:
1.Katzman MA, Bilkey TS, Chokka PR, et al. BMC Psychiatry. 2017;17:302. 2.McIntyre RS, Kennedy SH, Soczynska JK, et al. Prim Care Companion J Clin Psychiatry. 2010;12. 3.Tamam L, Karakus G, Ozpoyraz N. Eur Arch Psychiatry Clin Neurosci. 2008;258:385-93. 4.McIntosh D, Kutcher S, Binder C, et al. Neuropsychiatr Dis Treat. 2009;5:137-50. 5.Mattos P, Louza MR, Palmini AL, et al. J Atten Disord. 2013;17:444-8. 6.Takahashi N, Koh T, Tominaga Y, et al. World J Biol Psychiatry. 2014;15:488-98. 7.Canadian ADHD Resource Alliance. Canadian ADHD Practice Guidelines, 4th ed. Feb 2018. Available at: https://www.caddra.ca/wp-content/uploads/CADDRA-Guidelines-4th-Edition_-Feb2018.pdf (Accessed on January 24, 2020). 8.National Institute for Health and Care Excellence. Attention deficit hyperactivity disorder: diagnosis and management. March 2018. Available at: https://www.nice.org.uk/guidance/ng87 (Accessed on January 24, 2020).

CONCERTA® Extended-Release Tablets 18mg, 27mg, 36mg & 54mg
ABBREVIATED PRESCRIBING INFORMATION
ACTIVE INGREDIENT(S): Methylphenidate HCl. **INDICATION(S):** Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children ≥6 yrs, adolescents, and adults up to the age of 65. **DOSAGE & ADMINISTRATION:** Once daily in the morning. Swallow whole. Adults (18-65 yrs) new to methylphenidate, starting dose is 18 or 36 mg/day. Dosage may be increased by 18 mg/day at weekly intervals and should not exceed 72 mg/day for adults. Children (6-12 yrs) and adolescents (13-17 yrs) new to methylphenidate, starting dosage is 18 mg once daily. Dosage may be increased by 18 mg/day at weekly intervals and should not exceed 54 mg/day in children and 72 mg/day in adolescents. Patients currently using methylphenidate, dosing is based on current dose regimen and clinical judgment, see full prescribing information for recommended dose. **CONTRAINDICATIONS:** Known hypersensitivity to the product. Marked anxiety, tension, or agitation. Glaucoma. Motor tics or a family history or diagnosis of Tourette's syndrome. Patients currently using or within 2 weeks of using an MAO inhibitor. **SPECIAL WARNINGS & PRECAUTIONS:** CONCERTA should be given cautiously to patients with a history of drug dependence or alcoholism. Serious Cardiovascular Events: Stimulant products generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. Psychiatric Adverse Events: Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder. Particular care in using stimulants to treat ADHD in patients with comorbid bipolar disorder. Monitor for appearance of or worsening of aggressive behavior or hostility. Seizures: Stimulants may lower the convulsive threshold. Discontinue in the presence of seizures. Priapism: Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention. Peripheral Vasculopathy, including Raynaud's Phenomenon: Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Long-Term Suppression of Growth: Monitor growth in pediatric patients during treatment, and patients not growing or gaining height or weight as expected may need to have their treatment interrupted. Visual Disturbance: Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. Potential for Gastrointestinal obstruction: only be used in patients who are able to swallow the tablet whole. Hematologic monitoring: Periodic CBC, differential, and platelet counts are advised during prolonged therapy. Suicidal Tendency: Patients with emergent suicidal ideation or behavior during treatment for ADHD should be evaluated immediately by their physician. Consideration should be given to the exacerbation of any underlying psychiatric condition and to a possible causal role of methylphenidate treatment. **SIDE EFFECTS:** Children and adolescents: abdominal pain upper. Adults: decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, weight decreased, irritability, and hyperhidrosis. Refer to the full prescribing information for other side effects. **PREGNANCY & LACTATION:** Pregnancy Category C. Caution should be exercised if administered to nursing mothers. **INTERACTIONS:** MAO inhibitors. Vasopressors. Coumarin anticoagulants, anticonvulsants, and some antidepressants. **PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING.** API version to be quoted on promotional material: Concerta aPI ver.4.0

CP-136135 Feb 2020 4IC_1209

Janssen
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Unit 1302-1307, Tower 1, Grand Century Place,193 Prince Edward Road West,
Mongkok, Kowloon, Hong Kong
Tel: 2736 1711 Fax: 2736 1926

ONCE-DAILY CONCERTA®
methylphenidate HCl

Film Review
Shamans of the Blind Country – A film by Michael Oppitz

Dr Wai-ching YAN
MBChB (HK), FHKCPsych, FHKAM (Psychiatry)
Specialist in Psychiatry
Associate Consultant, Department of Psychiatry, Kowloon Hospital

Dr Wai-ching YAN

I well remember when we were in medical school, it was taught that for a proper physical examination, one should follow the sequence of inspection, palpitation, percussion and auscultation. The sequence cannot be altered (unless you want to fail your exam) and we practised over and over again with either our peers or real patients. When I was trained to be a psychiatrist, one of the first skills I was taught was the structure of a psychiatric history taking. I was asked to practice all the standard questions verbatim in order to elicit various psychopathologies. I memorised them hard enough to make sure I will not forget for the rest of my life.

After attaining my fellowship, I took up training as a psychotherapist. From the arrangement of my desk and chair, the way I and my client sit, to the intonation of my speech, every nuance is believed to influence the outcome of a session. I was coached by my supervisor to pay attention to every gesture of my clients, and to pick up important cues from my clients with appropriate reactions under the teaching of my psychotherapy school-of-thoughts. It took me a few years to master those skills before I became confident enough to lead a session with insightful communication with my clients.

From medical school to psychotherapy training, there have been loads of skills learning. The abilities to interact with patients properly, which we call soft skills, cannot be obtained from textbooks nor the internet. They were acquired through years of apprenticeship. So where did the apprenticeship begin? From where in history that a healer has started passing his skills to other people? Through what kind of ritualistic ceremony that skills of healing can be transferred from one generation to the next? If you are interested in tracing the origin, you could not possibly miss studying shamanism, which has been deeply rooted in almost every culture around the world.

Shamanism refers to the practice of a natural healer. Shamans have existed long before the birth of any civilisation and written language. Not many of us know what shamans exactly do because it is so varied across cultures. Moreover, very often, the training of being a shaman is through observation and oral teaching. The training details are difficult to be disseminated to outsiders. However, contrary to ordinary belief, the pathway to becoming a shaman can be extremely tedious. The chosen student has to go through a journey of rituals and trainings before he could be recognised as a shaman.

Because of self-protection as well as isolation from the modern world, it has been difficult for outsiders to study how a shaman is trained. Therefore, in order to have a glimpse of what shamanism is about, visual images are the best form of media that amateurs like us can depend on. Here I would like to recommend an epic documentary filmed by Michael Oppitz, who has provided the first vivid and in-depth look into this mysterious Shamanic training in a rural part of Nepal.

Michael Oppitz is an anthropologist and sinologist. From 1992 till 2008, he was a professor at the University of Zurich/Switzerland and Director of the Ethnographic Museum Zurich. Much early on in 1965, he came to Nepal for the first time and studied faith healers in a remote mountain region of north-western Nepal. Based on having spent years observing and living with the people there, he directed the four-hour documentary Shamans of the Blind Country in the 1970s with great impact on our understanding of shamanism. The film was first shown in Berlin Film Festival in 1981 with great success. Thirty-odd years later, a digitally remastered version was put on screen in the 64th Berlin Film Festival.

The documentary shows shamanism in a Himalayan community called Magar. The documentary follows the arduous process of initiation that each student has to go through before he or she can be chosen as healers. The film captures many rituals the shamans perform to cure their patients' illnesses and to avert their misfortune. The film is both comprehensive and largely observational. Any facets of this shamanism are presented in a visual language that suits the Magar perspective, disregarding all theoretical explanation that usually happens in this kind of ethnographic films.

The documentary comprises two Parts. Part I displays a variety of healing rituals carried out by the shamans in the Dhaulagiri region. Part II focuses on the transmission of the shaman's knowledge from master to student. The transmission is by the oral route, hence no books involved. It all happens in vicarious learning, where the student is requested to watch and imitate the master's performance. The performance is complicated involving the manufacture of the required tools, preparation of a sacred spot or altar, conducting the operations in the right order, and above all, learning the mythical chants, the original stories and auxiliary chants, echoing the master line by line to the beat of his drum. You can imagine it takes a very long time to master those skills especially when there is no written language in the Magar community.

This four-hour documentary is definitely not the Hollywood type of movies which are filled with superheroes' flying and fighting against each other. It demands both your attention span and patience. However, if you can immerse yourself in a culture of shamanism, you may try to compare their ritualistic practice with our modern medicine. It is always fun to compare and you will be amazed to see the similarities.

Feel Better...
Think Better! Do Better!

Lundbeck

Lundbeck HK Limited
Suite 4303, Central Plaza,
18 Harbour Road, Wanchai, Hong Kong
Tel: 2244 8888 Fax: 2827 2228
www.lundbeck.com

Brintellix®
vortioxetine

For the treatment of major depressive episodes in adults

BRINTELLIX® (VORTIOXETINE) – ABBREVIATED PRESCRIBING INFORMATION
Presentation: Film-coated tablets 5mg, 10mg and 20mg. **Indication:** Treatment of major depressive episodes in adults. **Dosage:** Adults: starting and recommended dose is 10mg, once-daily, taken with or without food. Elderly ≥65 years: Starting dose 5mg. Children and adolescents (<18 years): should not be used. Discontinuation: Patients can abruptly stop taking the medicinal product without the need for a gradual reduction in dose. **Contraindications:** Hypersensitivity to vortioxetine or to any of the excipients. Combination with MAO-inhibitors. Should not be used during pregnancy or lactation unless clearly needed and after careful consideration of the risk/benefit. **Special warnings and precautions:** Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide. It is a general clinical experience that the risk of suicide may increase in the early stages of recovery. Close supervision of high-risk patients should accompany drug therapy. Patients (and caregivers) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present. Should be introduced cautiously in patients who have a history of seizure or in patients with unstable epilepsy. Patients should be monitored for the emergence of signs and symptoms of Serotonin Syndrome or Neuroleptic Malignant Syndrome. Should be used with caution in patients with a history of mania/hypomania and should be discontinued in any patient entering a manic phase. There have been reports of cutaneous bleeding abnormalities with the use of SSRIs/SNRIs. Hyponatraemia has been reported rarely with the use of SSRIs/SNRIs Caution should be exercised for patients with renal or hepatic impairment. **Interactions:** Caution is advised when taken in combination with MAO-inhibitors, serotonergic medicinal products, products lowering the seizure threshold, lithium, tryptophan, St. John's Wort, oral anticoagulants or antiplatelet agents, and products predominantly metabolised by the enzymes CYP2D6, CYP3A4, CYP2C9 and Cytochrome P450. **Undesirable effects:** Adverse reactions are most frequent during the first or second week of treatment and usually decrease in intensity and frequency with continued treatment. Very common: Nausea. Common: abnormal dreams, dizziness, diarrhoea, constipation, vomiting, pruritus, including pruritus generalised. Uncommon: flushing, night sweats. Unknown: Serotonin Syndrome. **Overdose:** Symptomatic treatment. Marketing authorisation holder: Lundbeck HK Limited. Revision Date: May 2017. Full prescribing information is available upon request.

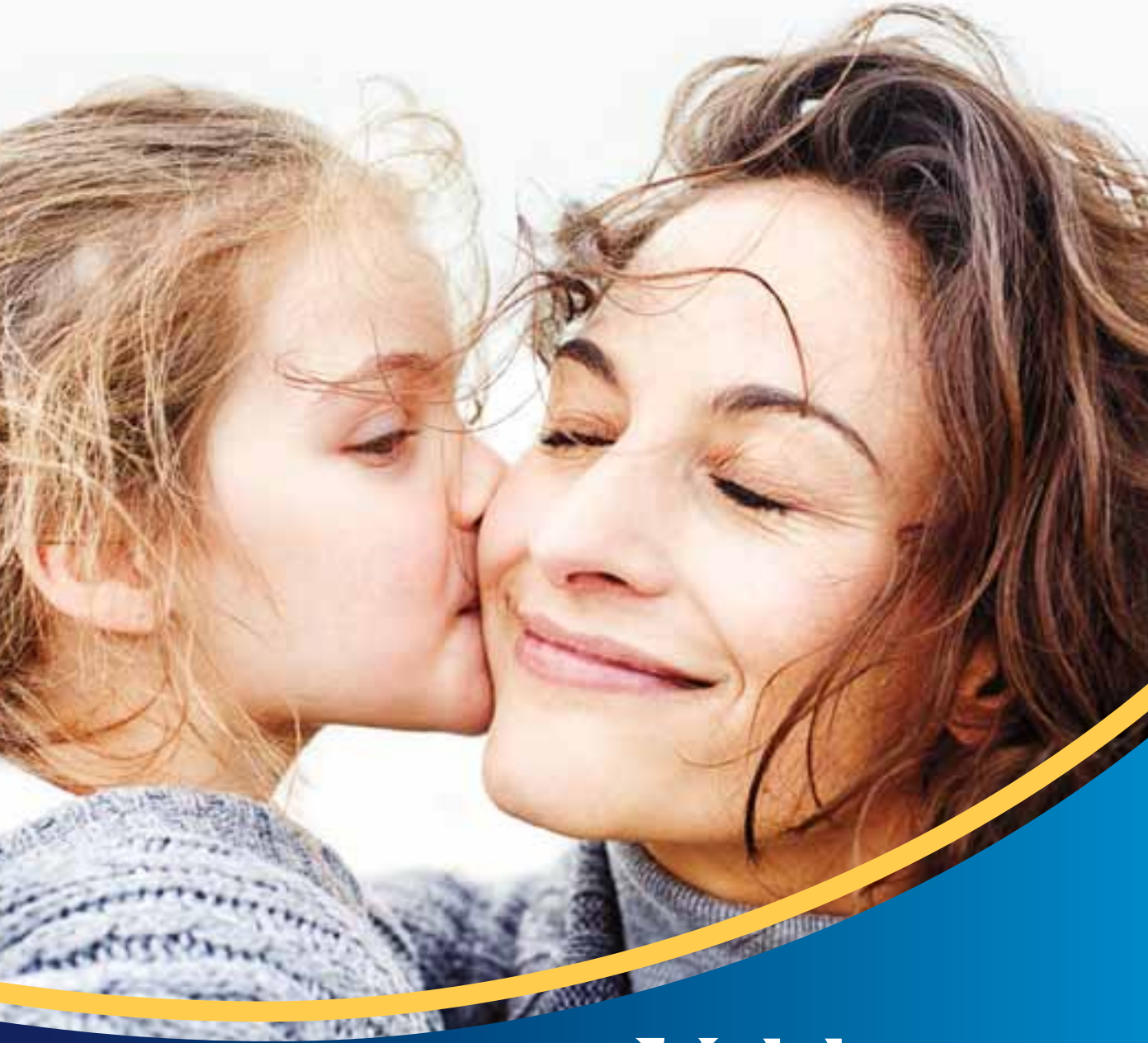
HK-BRIN-2019.08-AD05-MPL

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
* Primary Care Forum 1	2	* HKMA-HKS&H CME Programme 2019-2020 Topic: Surgical Treatment of Urological Cancers * HKMA Council Meeting 3	* Certificate Course on Update in Clinical Sleep Medicine 2020 4	* Certificate Course in Cardiology 2020 5	6	* Refresher Course for Health Care Providers 2019/2020 - Caring for elderlies in family practice 7
8	9	* Colorectal Cancer Prevention and Treatment Updates * 1) Management of Hypertension with Vasodilating Beta-blockers 2) Update on the Management of Erectile Dysfunction 10	* Certificate Course on Neurology * Certificate Course on Update in Clinical Sleep Medicine 2020 11	* Hearing Loss - A Microscopic View * Palliative Home Care in the Eye of Family Physicians * Certificate Course in Cardiology 2020 12	13	* Mastering Adverse Outcomes 14
15	16	17	* Certificate Course on Neurology * Building Resilience and Avoiding Burnout * Certificate Course on Update in Clinical Sleep Medicine 2020 18	* Legal Aspect of End of Life Care * Childhood Anxiety Disorder * Certificate Course in Cardiology 2020 * FMSHK Executive Committee Meeting 19	* Dementia Revisited: New "Kids" on Board Helpful for Diagnosis and Treatment * Better HT Management with the Right SPC: from Control to Protection 20	* Certificate Course on Lower Urinary Tract Symptoms (LUTS) management 21
22	23	* 1) Advanced in Neurorehabilitation * Mastering Your Risk 24	* Certificate Course on Neurology 25	* Leading the Shift in Paradigm in T2D Treatments: Cardio-Protection with Glucose-Lowering Drug * Certificate Course for GPs 2020 - The Role of the General Practitioner in Heart Failure: from Diagnosis to Palliative Care 26	* Non Surgical Treatment of Benign Thyroid Nodule 27	* Achieving Safer and Reliable Practice 28
29	30	* Sarcopenia and Frailty * Mastering Shared Decision Making 31				

Date / Time	Function	Enquiry / Remarks
1 SUN 9:00 PM	**Primary Care Forum** **1. Incidence of Type II Diabetes in Chronic Obstructive Pulmonary Disease (COPD)** **2. Opportunities to diagnose COPD at an earlier stage in primary care** **3. Update in Asthma Clinical Practice Guidelines (GINA, 2019)** **4. SABA: An appropriate reliever in asthma?** **5. How to achieve high vaccination rate in primary care?** **6. Helicobacter pylori testing and treatment in primary care** **7. Optimizing the management of IBS-C** Organiser: Hong Kong Medical Association; Speaker: Dr. Hugo TAN, Dr. YU Wai Cho, Dr. Thomas YW MOK, Dr. Matthew WONG, Prof. Fanny KO, Prof. Ivan HUNG & Dr. Michael KS CHEUNG; Venue: Eaton Hotel	HKMA CME Department 2527 8452 3 CME Points
3 TUE 1:00 PM	**HKMA-HKS&H CME Programme 2019-2020** **Topic: Surgical Treatment of Urological Cancers** Organiser: Hong Kong Medical Association & Hong Kong Sanatorium & Hospital; Speaker: Dr. YIU Ming Kwong; Venue: The HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai	HKMA CME Department 2527 8452 1 CME Point
9:00 PM	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Christine WONG Tel: 2527 8285
4 WED 7:00 PM	**Certificate Course on Update in Clinical Sleep Medicine 2020** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
5 THU 7:00 PM	**Certificate Course in Cardiology 2020** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
7 SAT 2:15 PM	**Refresher Course for Health Care Providers 2019/2020 -** **Caring for elderlies in family practice** Organiser: Hong Kong Medical Association, HK College of Family Physicians & HA-Our Lady of Maryknoll Hospital; Speaker: Dr. LAM Wing Wo; Venue: Lecture Halls A&B, 4/F, Block G, Wong Tai Sin Hospital	Ms. Clara TSANG 2354 2440 2 CME Points
10 TUE 1:00 PM	**Colorectal Cancer Prevention and Treatment Updates** Organiser: HKMA-YTM Community Network; Speaker: Dr. CHOW Man Po; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon	Ms. Candice TONG 2527 8285 1 CME Point
1:00 PM	**1) Management of Hypertension with Vasodilating Beta-blockers** **2) Update on the Management of Erectile Dysfunction** Organiser: HKMA-Tai Po Community Network; Speaker: Dr. CHEUNG Shing Him & Dr. CHAN Lung Wai; Venue: Jade Garden, Shop 302, 3/F, Tai Wo Plaza Phase 1, 12 Tai Wo Road, Tai Wo	Ms. Candice TONG 2527 8285 2 CME Points
11 WED 1:00 PM	**Certificate Course on Neurology** **1) Dementia Journey From Practical Management to Case Sharing** Organiser: HKMA-Central, Western & Southern Community Network; Speaker: Dr. LUI Wing Cheong, Victor; Venue: The HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central	Miss Antonia LEE 2527 8285 1 CME Point
7:00 PM	**Certificate Course on Update in Clinical Sleep Medicine 2020** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
12 THU 1:00 PM	**Hearing Loss - A Microscopic View** Organiser: HKMA-New Territories West Community Network; Speaker: Dr. CHOW Siu Wah, Jennifer; Venue: Pak Loh Chiu Chow Restaurant, Shop A316, 3/F, Yoho Mall II, 8 Long Yat Road, Yuen Long	Miss Antonia LEE 2527 8285 1 CME Point
1:00 PM	**Palliative Home Care in the Eye of Family Physicians** Organiser: HKMA-HK East Community Network & Haven of Hope Christian Service; Speaker: Dr. CHAN Hung Wai, Patrick, Dr. TSANG Chiu Yee, Luke & Dr. KONG Wing Ming, Henry; Venue: The HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai	Ms. Candice TONG 2527 8285 1 CME Point
7:00 PM	**Certificate Course in Cardiology 2020** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
14 SAT 2:30 PM	**Mastering Adverse Outcomes** Organiser: Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. CHENG Ngai Shing, Justin; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Department 2527 8452 3 CME Points
18 WED 1:00 PM	**Certificate Course on Neurology** **2) Prevention Strategies and Treatments for Migraine and Headache** Organiser: HKMA-Central, Western & Southern Community Network; Speaker: Dr. TSANG Kin Lun; Venue: The HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central	Miss Antonia LEE 2527 8285 1 CME Point
6:30 PM	**Building Resilience and Avoiding Burnout** Organiser: Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. FUNG Shu Yan, Anthony; Venue: The Cityveiw, 23 Waterloo Road, Kowloon, Hong Kong	HKMA CME Department 2527 8452 3 CME Points
7:00 PM	**Certificate Course on Update in Clinical Sleep Medicine 2020** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
19 THU 1:00 PM	**Legal Aspect of End of Life Care** Organiser: HKMA-HK East Community Network & Haven of Hope Christian Service; Speaker: Ms. Olivia LEUNG; Venue: The HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai	Ms. Candice TONG 2527 8285 1 CME Point
1:00 PM	**Childhood Anxiety Disorder** Organiser: HKMA-KLN East Community Network; Speaker: Dr. LIN Hoi Yun, Candy; Venue: V Cuisine, 6/F, Holiday Inn Express Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O	Miss Antonia LEE 2527 8285 1 CME Point

Date / Time	Function	Enquiry / Remarks
19 THU 7:00 PM	**Certificate Course in Cardiology 2020** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
20 FRI 1:00 PM	**Dementia Revisited: New "Kids" on Board Helpful for Diagnosis and Treatment** Organiser: HKMA-KLN City Community Network; Speaker: Dr. CHAN Chun Chung, Ray; Venue: President's Room, Spotlight Recreation Club, 4/F, Screen World, Site 8, Whampoa Garden, Hunghom, Kowloon	Ms. Candice TONG 2527 8285 1 CME Point
1:00 PM	**Better HT Management with the Right SPC: from Control to Protection** Organiser: HKMA-Shatin Community Network; Speaker: Dr. Norman CHAN; Venue: Sapphire Room, Level 2 Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Candice TONG 2527 8285 1 CME Point
21 SAT 1:00 PM	**Certificate Course on Lower Urinary Tract Symptoms (LUTS) management** **4. LUTS Management (Tips And Risk In Primary Care Setting)** **5. LUTS And Anticholinergic Burden (ACB)** **6. LUTS and Heart Diseases** Organiser: Hong Kong Medical Association & Hong Kong Elderly Welfare Foundation; Speaker: Dr. MAK Siu King. Dr. Jennifer Ma Wai Wai MYINT & Dr. WONG Tai Hung, John; Venue: Telemedicine and Conference Hall, 29/F, International Medical Centre, One Chinachem Central, 22 Des Voeux Road Central, Hong Kong (MTR Central Station Exit C)	HKMA CME Department 2527 8452 2 CME Points
24 TUE 1:00 PM	**1) Advanced in Neurorehabilitation; 2) Cognitive Assessment in Clinic** Organiser: HKMA-Tai Po Community Network; Speaker: Prof. WONG Ka Sing, Lawrence & Dr. CHUANG Lai; Venue: Jade Garden, Shop 302, 3/F, Tai Wo Plaza Phase 1, 12 Tai Wo Road, Tai Wo	Ms. Candice TONG 2527 8285 2 CME Points
6:30 PM	**Mastering Your Risk** Organiser: Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. LEE Wai Hung, Danny; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Department 2527 8452 3 CME Points
25 WED 1:00 PM	**Certificate Course on Neurology** **3) The Update of Parkinson's Disease** Organiser: HKMA-Central, Western & Southern Community Network; Speaker: Dr. TSANG Kin Lun; Venue: The HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central	Miss Antonia LEE 2527 8285 1 CME Point
26 THU 1:00 PM	**Leading the Shift in Paradigm in T2D Treatments: Cardio-Protection with Glucose-Lowering Drug** Organiser: HKMA-New Territories West Community Network; Speaker: Dr. LAU Chun Leung; Venue: Atrium Function Rooms, Lobby Floor, Hong Kong Gold Coast Hotel, 1 Castle Peak Road, Gold Coast, Hong Kong	Miss Antonia LEE 2527 8285 1 CME Point
1:00 PM	**Certificate Course for GPs 2020 - The Role of the General Practitioner in Heart Failure: from Diagnosis to Palliative Care** Organiser: HKMA-KLN East Community Network, HA-United Christian Hospital & HK College of Family Physicians; Speaker: Dr. Andrew LI; Venue: Lecture Theatre, G/F, Block K, United Christian Hospital	Ms. Phoebe WONG 3949 3079 1 CME Point
27 FRI 1:00 PM	**Non Surgical Treatment of Benign Thyroid Nodule** Organiser: HKMA-YTM Community Network; Speaker: Dr. KAN Mei Yee, Daisy; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon	Ms. Candice TONG 2527 8285 1 CME Point
28 SAT 2:30 PM	**Achieving Safer and Reliable Practice** Organiser: Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. CHENG Ngai Shing, Justin; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Department 2527 8452 3 CME Point
31 TUE 1:00 PM	**Sarcopenia and Frailty** Organiser: HKMA-KLN West Community Network; Speaker: Dr. CHUANG Lai & Dr. CHAN Fei; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chuen	Miss Antonia LEE 2527 8285 1 CME Point
6:30 PM	**Mastering Shared Decision Making** Organiser: Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. CHENG Ngai Shing, Justin; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Department 2527 8452 3 CME Point

That smile is not only for the kiss



Treatment of major depressive episodes in adults*

One tablet daily at bedtime

Valdoxan®

agomelatine

Re-emerging life

Composition*: Valdoxan 25 mg: film-coated tablet containing 25 mg of agomelatine. Contains lactose as an excipient. **Indications***: Treatment of major depressive episodes in adults. **Dosage and administration***: The recommended dose is 25 mg once daily taken orally at bedtime. After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50 mg once daily. Liver function tests should be performed in all patients before starting treatment. Treatment should not be initiated if transaminases exceed 3T upper limit of normal (see "Contraindications" and "Warnings" sections). During treatment, transaminases should be monitored periodically after around three weeks, six weeks (end of acute phase), twelve weeks and twenty four weeks (end of maintenance phase) and thereafter when clinically indicated (see "warnings" section). Treatment should be discontinued if transaminases exceed 3T upper limit of normal (see "Contraindications" and "Warnings" sections). When increasing the dosage, liver function tests should again be performed at the same frequency as when initiating treatment. Decision of dose increase has to be balanced with a higher risk of transaminases elevation. Any dose increase to 50 mg should be made on an individual patient benefit/risk basis and with strict respect of LFT monitoring. Patients should be treated for at least 6 months. **Contraindications***: Hypersensitivity to the active substance or to any of the excipients. Hepatic impairment (i.e. cirrhosis or active liver disease) or transaminases exceeding 3T upper limit of normal (see "Posology" and "Warnings" sections). Concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) (see "Interaction" section). **Warnings***: Cases of liver injury, including hepatic failure (few cases were exceptionally reported with fatal outcome or liver transplantation in patients with hepatic risk factors), elevations of liver enzymes exceeding 10 times upper limit of normal, hepatitis and jaundice have been reported in patients treated with Valdoxan. Monitoring of liver function: Before starting treatment: Treatment with Valdoxan should only be prescribed after careful consideration of benefit and risk in patients with hepatic injury risk factors e.g. obesity/overweight/non-alcoholic fatty liver disease, diabetes, alcohol use disorder and /or substantial alcohol intake and in patients receiving concomitant medicinal products associated with risk of hepatic injury. Baseline liver function tests should be undertaken in all patients and treatment should not be initiated in patients with baseline values of ALT and/or AST >3 X upper limit of normal. Caution should be exercised when Valdoxan is administered to patients with pretreatment elevated transaminases (> the upper limit of the normal ranges and ≤3 times the upper limit of the normal range). Frequency of liver function tests: liver function tests should be performed in all patients (see "Posology" section). Any patient who develops increased serum transaminases should have his/her liver function tests repeated within 48 hours. During treatment period: Valdoxan treatment should be discontinued immediately if patient develops symptoms or signs of potential liver injury, if the increase in serum transaminases exceeds 3 X upper limit of normal. Following discontinuation of Valdoxan therapy liver function tests should be repeated until serum transaminases return to normal. Patients under 18 years of age: not recommended. Elderly patients (≥75 years): should not be used. Elderly patients with dementia: should not be used. Bipolar disorder/mania/hypomania: used with caution and discontinued if maniac symptoms appear. Suicide/suicidal thoughts: patients should be closely monitored. Combination with potent CYP1A2 inhibitors: contraindicated. Excipients: contains lactose. **Interaction(s)***: Contra-indicated: potent CYP1A2 inhibitors. Not recommended: alcohol; moderate CYP1A2 inhibitors. **Fertility*, Pregnancy***: Not recommended. **Breastfeeding***: With precautions. **Drive & Use Machines***: Possible occurrence of dizziness and somnolence should be taken into account. **Undesirable Effects***: Very common: headache. Common: Anxiety, abnormal dreams, dizziness, somnolence, insomnia, nausea, diarrhoea, constipation, abdominal pain, vomiting, increased ALAT and/or ASAT, back pain, fatigue, weight increased. Uncommon: Suicidal thoughts or behavior, agitation, irritability, restlessness, aggression, nightmares mania/hypomania, confusional state, migraine, paraesthesia, restless leg syndrome, blurred vision, tinnitus, increased gamma-glutamyltransferase, hyperhidrosis, eczema, pruritus, urticaria, weight decreased. Rare: Hallucinations, akathisia, hepatitis, increased alkaline phosphatase, hepatic failure, jaundice, erythematous rash, face oedema and angioedema, urinary retention. **Overdose***, **Properties***: Agomelatine is a melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist. Agomelatine resynchronises circadian rhythms in animal models of circadian rhythm disruption. Agomelatine increases noradrenaline and dopamine release specifically in the frontal cortex and has no influence on the extracellular levels of serotonin. **Presentation***: Pack of 28 film-coated tablets of Valdoxan 25 mg. **Les Laboratoires Servier**, 50 rue Carnot, 92284 Suresnes cedex France. **www.servier.com**

VAL20001D Jan/2020

SERVIER

SERVIER HONG KONG LIMITED
Room 4201-03, 42/F, Sunlight Tower, 248 Queen's Road East, Wan Chai, Hong Kong. Tel: (852) 2577 1922 Fax: (852) 2890 5703 www.servier.hk

Answers to Dermatology Quiz

Answers:

1. Malignant acral lentiginous melanoma, Pigmented basal cell carcinoma, Secondary cutaneous metastasis, Dysplastic naevus, Squamous cell carcinoma and so on can be the possible differential diagnoses.

   Malignant acral lentiginous melanoma is a subtype of malignant melanoma which is more commonly found amongst Asian and sub-Saharan African. It is due to the development of malignant melanocytes along the basal layer of the epidermis. These malignant cells may arise from an existing melanocytic naevus or more often, de novo, from previously normal-appearing skin.

2. Dermoscopy by a trained doctor can be helpful to find clues such as asymmetrical structure and colours, multi-component pattern, parallel ridge pattern and diffuse pigmentation of different shades of brown colours suggesting melanoma. Skin biopsy is still necessary for differentiating the above-mentioned differential diagnoses and confirming malignant melanoma. Although no single histologic feature is pathognomonic for melanoma, there are few characteristic features such as cytologic atypia with enlarged cells with numerous mitotic figures. Immunohistochemical stains such as S-100 and homatropine methylbromide (HMB 45) can help to differentiate melanoma from other lesions.

3. For small and primary malignant melanoma, wide excision is the mainstay of treatment. Sentinel lymph node biopsy should be offered if the melanoma is thick. For advanced disease, chemotherapy may be needed, especially for wide-spreading disease. Nowadays, immunotherapy and biologics such as ipilimumab and BRAF inhibitors, in which around 60% of melanoma has BRAF mutation, such as vemurafenib, dabrafenib and trametinib are all recently approved by FDA in treatment of unresectable or metastatic BRAF mutation melanoma are showing the promising result.

Dr Chi-keung KWAN
MBBS(HK), FRCP(Lond, Glasg), Dip Derm(Glasg), PDipID(HK), FHKCP, FHKAM(Med)
Specialist in Dermatology and Venereology

Betmiga®
mirabegron

THE *1ST* β_3-AGONIST FOR **OAB* PATIENTS**
WITH PROMISING SAFETY PROFILE
PLACEBO-LIKE DRY MOUTH(1.7%) SIDE EFFECT[1]

Harnal OCAS®
tamsulosin

YOUR *1ST* STEP FOR **MALE LUTS+ PATIENTS**
WITH PROMISING SAFETY PROFILE#
PLACEBO-LIKE DIZZINESS(1.4%) SIDE EFFECT[2]

A *FRESH* STEP IN LUTS+ MANAGEMENT

*OAB: Overactive Bladder + LUTS: Lower Urinary Tract Symptoms
α_1-blockers are often considered the first line drug treatment of male LUTS[3]

Reference: **1.** Chapple C.R. et al. Neurourol Urodynam 2013 [doi 10.1002/nau22505] **2.** Chapple C.R. et al. Eur Urol Supp. 2005; 4:33-44
3. Gravas S, et al. EAU Guidelines on the Treatment of Non-neurogenic Male LUTS. European Association of Urology. 2017.

Abbreviated prescribing information of Harnal OCAS® 0.4 mg Tablets
Version: 002 PI version: Sep 2013. **Composition:** Tamsulosin HCl **Indication:** Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). **Dosage:** 1 tab daily, can be taken independently of food. **Administration:** Swallow whole, do not chew/crunch. **Contraindications:** Hypersensitivity to tamsulosin hydrochloride or to any of the excipients. **Special warnings and special precaution for use:** As with other α1-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with Harnal OCAS® 0.4 mg Tablets, as a result of which, rarely, syncope can occur. At the first signs of orthostatic hypotension (dizziness, weakness), the patient should sit or lie down until the symptoms have disappeared. Before therapy with Harnal OCAS® 0.4 mg Tablets is initiated, the patient should be examined in order to exclude the presence of other conditions, which can cause the same symptoms as benign prostatic hyperplasia. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards. Treatment of patients with a history of orthostatic hypotension should be approached with caution. The treatment of patients with severe renal impairment (creatinine clearance of <10 ml/min) should be approached with caution, as these patients have not been studied. The treatment of patients with severe hepatic dysfunction should be approached with caution. The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been observed during cataract and glaucoma surgery in some patients on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after the operation. Discontinuing tamsulosin hydrochloride 1-2 weeks prior to cataract or glaucoma surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not been established. IFIS has also been reported in patients who had discontinued tamsulosin for a longer period prior to the surgery. The initiation of therapy with tamsulosin hydrochloride in patients for whom cataract or glaucoma surgery is scheduled is not recommended. During pre-operative assessment, surgeons and ophthalmic teams should consider whether patients scheduled for cataract or glaucoma surgery are being or have been treated with tamsulosin in order to ensure that appropriate measures will be in place to manage the IFIS during surgery. Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype. Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4. Cases of allergic reaction to tamsulosin in patients with a past history of sulfonamide allergy have been reported. If a patient reports a previously experienced sulfa allergy, caution is warranted when administrating tamsulosin hydrochloride. **Undesirable effects:** *Common (>1%, <10%), Uncommon (>0.1%, <1%), Rare (>0.01%, <0.1%), Very rare (<0.01%). Cardiac disorder: Uncommon:* Palpitations. *Gastrointestinal disorders: Uncommon:* Constipation, diarrhoea, nausea, vomiting. *General disorders and administration site conditions: Uncommon:* Asthenia. *Nervous systems disorders: Common:* Dizziness (1.3%). *Uncommon:* Headache. *Rare: Syncope. Reproductive system and breast disorders: Common:* Ejaculation disorders. *Very rare:* Priapism. *Respiratory, thoracic and mediastinal disorders: Uncommon:* Rhinitis. *Skin and subcutaneous tissue disorders: Uncommon:* Rash, pruritus, urticaria. *Rare:* Angioedema. *Vascular disorders: Uncommon:* Orthostatic hypotension. ***Post-marketing experience:*** The following events have also been reported during the post-marketing period. These events are reported voluntarily from a population of uncertain size, therefore it is not possible to reliably estimate their frequency: visual disorders (e.g. blurred vision, visual impairment), dermatitis exfoliative, erythema multiforme and epistaxis. During cataract and glaucoma surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been reported. **Full prescribing information is available upon request.**

Abbreviated prescribing information of Betmiga® prolonged-release tablets
Version: 003 PI version: Apr 2016. **Composition:** Mirabegron **Indication:** Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. **Dosage:** Adult including elderly 50 mg once daily with or without food. **Administration:** Swallow whole with liquids. Do not chew/divide/crush. **Contraindications:** Mirabegron is contraindicated in patients with - Hypersensitivity to the active substance or to any of the excipients. - Severe uncontrolled hypertension defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg. **Special warnings and precautions for use:** Renal impairment: Betmiga has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m^2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2); based on a pharmacokinetic study a dose reduction to 25 mg is recommended in this population. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2) concomitantly receiving strong CYP3A inhibitors. Hepatic impairment: Betmiga has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. Betmiga is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors. Hypertension: Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with Betmiga, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg). Patients with congenital or acquired QT prolongation: Betmiga, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients. Patients with bladder outlet obstruction and patients taking antimuscarinics medications for OAB: Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with Betmiga; however, Betmiga should be administered with caution to patients with clinically significant BOO. Betmiga should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB. **Undesirable effects:** Summary of the safety profile: The safety of Betmiga was evaluated in 8,433 patients with OAB, of which 5,648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received Betmiga for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with Betmiga, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity. The most common adverse reactions reported for patients treated with Betmiga 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving Betmiga 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving Betmiga 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving Betmiga 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving Betmiga 50 mg. Serious adverse reactions included atrial fibrillation (0.2%). Adverse reactions observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies. List of adverse reactions: The table below reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Infections and infestations: Common: Urinary tract infection. Uncommon: Vaginal infection, Cystitis. Psychiatric disorders: Not known (cannot be estimated from the available data): Insomnia*. Eye disorders: Rare: Eyelid oedema. Cardiac disorders: Common: Tachycardia. Uncommon: Palpitation, Atrial fibrillation. Vascular disorders: Very rare: Hypertensive crisis*. Gastrointestinal disorders: Common: Nausea*, Constipation*, Diarrhoea*. Uncommon: Dyspepsia, Gastritis. Rare: Lip oedema. Skin and subcutaneous tissue disorders: Uncommon: Urticaria, Rash, Rash macular, Rash popular, Pruritus. Rare: Leukocytoclastic vasculitis, Purpura, Angioedema*. Musculoskeletal and connective tissue disorders: Uncommon: Joint swelling. Reproductive system and breast disorders: Uncommon: Vulvovaginal pruritus. Investigations: Uncommon: Blood pressure increased, GGT increased, AST increased, ALT increased. Renal and urinary disorders: Rare: Urinary retention*. Nervous system disorders: Common: Headache*, Dizziness*. *observed during post-marketing experience. **Full prescribing information is available upon request.**

Astellas Pharma Hong Kong Co., Ltd. Unit 1103-08, 11/F, Tower 1, Grand Century Place, 193 Prince Edward Road West, Mongkok, Kowloon.
Tel: (852) 2377 9801 Fax: (852) 2856 1440

astellas | UROLOGY Commitment in Urology

BET-MAD-0501118-0001

Ketosteril®

Gain Precious Time

Ketosteril®-supplemented vegetarian very low protein diet (sVLPD) could defer dialysis initiation by ameliorating metabolic disturbances associated with chronic kidney disease (CKD)[1]

Name of the medicinal product: Ketosteril® film-coated tablets. **Composition:** One film-coated tablet contains: (DL)-3-methyl-2-oxovaleric acid (α-ketoanalogue to DL-isoleucine, Ca-salt) 67 mg; 4-methyl-2-oxovaleric acid (α-ketoanalogue to leucine, Ca-salt) 101 mg, 2-oxo-3-phenylpropionic acid (α-ketoanalogue to phenylalanine, Ca-salt) 68 mg, 3-methyl-2-oxo-butyric acid (α-ketoanalogue to valine, Ca-salt) 86 mg, (DL)-2-hydroxy-4-methylthio-butyric acid (α-hydroxyanalogue to DL-methionine, Ca-salt) 59 mg, L-lysine acetate 105 mg (= 75 mg L-lysine), L-threonine 53 mg, L-tryptophan 23 mg, L-histidine 38 mg, L-tyrosine 30 mg, total nitrogen content per tablet 36 mg, calcium content per tablet 1.25 mmol = 50 mg. Excipients: Maize starch, crospovidone type A, talc, silica (colloidal anhydrous), magnesium stearate (Ph.Eur) [vegetable], macrogol 6000, quinoline yellow E104, basic butyla-ted methacrylate copolymer, triacetine, titanium dioxide E171, povidone K 29-32. **Therapeutic indications:** Prevention and treatment of damages due to faulty or deficient protein metabolism in chronic kidney disease in connection with a limited dietary protein intake of 40 g/day or less (adult). Usually this applies to patients whose glomerular filtration rate (GFR) is less than 25 ml/min. **Posology and method of administration: I**f not otherwise prescribed the dose for adults (70 kg body weight) is 4 to 8 tablets three times daily during meals. The tablets must not be chewed. **I**ngestion during meals facilitates proper absorption and the metabolisation into the corresponding amino acids. **Contraindications:** Hyper-sensitivity to the active substances or to any of the excipients, hypercalcae-mia and disturbed amino acid metabolism. **Special warnings and precautions for use:** The serum calcium level should be monitored regularly. A sufficient supply of calories should be ensured. No experience has been gained so far with the administration in paediatric patients. **I**n the presence of hereditary phenylketonuria, attention should be given to the fact that Ketosteril® contains phenylalanine. Monitoring of the serum phosphate levels is needed in case of concomitant administration of aluminium hydroxide. **Interaction with other medicinal products and other forms of interaction:** Concomitant administration of calcium-containing drugs may cause or aggravate elevated serum calcium levels. Drugs that form hardly soluble compounds with calcium (e.g. tetracyclines, quinolines such as ciprofloxacin and nor-floxacin as well as drugs containing iron, fluoride or estramustine) should not be taken at the same time with Ketosteril® to avoid disturbed absorption of the active substances. An interval of at least two hours should elapse between the ingestion of Ketosteril® and these drugs. The susceptibility to cardioactive glycosides, and hence the risk for arrhythmia will increase if Ketosteril® produces elevated serum calcium levels. Uraemic symptoms improve under therapy with Ketosteril®. Thus, in case of aluminium hydroxide administration, the dose of this drug has to be reduced if necessary. Serum phosphate levels should be monitored for a decrease. **Pregnancy and lactation:** There are no adequate data from the use of Ketosteril® in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women. No experience has been made so far with the use during lactation. **Undesirable effects:** The intake of Ketosteril® may very rarely lead to hypercalcaemia. **I**f hypercalcaemia occurs, the intake of vitamin D should be reduced. **I**n case of persisting hypercalcaemia, the dose of Ketosteril® as well as the intake of any other calcium sources has to be reduced. **Overdose:** No case of overdose has been reported. **Special precautions for handling/storage:** Do not use Ketosteril® after expiry date! Keep out of the reach of children! Do not store above 25ºC. Store in the original package and keep the blisters tightly closed to protect contents from moisture.
Issue of information March 2009.

Reference code : 796837/03
Reference : 1 Garneata L et al. JASN 2016

FRESENIUS KABI
caring for life

Fresenius Kabi Hong Kong Ltd.
Room 5001-5027, 50/F, Sun Hung Kai Centre,
30 Harbour Road, Wanchai, Hong Kong
Tel : (852) 2152 1330 Fax : (852) 2119 0815
www.fresenius-kabi.com

HK-DA-004-2020